FORMULATION AND EVALUATION OF LOSARTAN POTASSIUM SUSTAINED RELEASE FLOATING TABLETS

Dissertation Submitted to

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In partial fulfillment of the requirement for the award of degree of

MASTER OF PHARMACY

In

PHARMACEUTICS

by
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UNDER THE GUIDANCE OF
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TAMIL NADU

APRIL 2013

DEDICATED

TO

MY

BELOVED PARENTS,

TEACHERS,

&

MY

DEARST

FRIENDS

CERTIFICATE

This is to certify that the dissertation entitled **“FORMULATION AND EVALUATION OF LOSARTAN POTASSIUM SUSTAINED RELEASE FLOATING TABLETS”** is a bonafide and genuine research work carried out at the Department of Pharmaceutics, K.K.College of pharmacy by **MEKANABOINA GANGADHAR, M.Pharm.,** during the year 2012-2013 under the supervision of **Mrs. M.Vani, M.Pharm., Asst.Prof.** Department of Pharmaceutics, K.K. College of Pharmacy, Chennai-600122. This dissertation is submitted for partial fulfillment of the requirement for the award of degree of Master of Pharmacy (Pharmaceutics), by the Tamil Nadu Dr. M.G.R Medical University, Chennai-32.

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MEKANABOINA GANGADHAR

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LIST OF ABBREVIATIONS

Sl. no.	Abbreviation	Full form
1.	Mcc	Micro crystalline cellulose
2.	Abs	Absorbance
3.	ACE	Angiotensin converting enzyme
4.	Avg	Average
5.	API	Active Pharmaceutical Ingredient
6.	AT	Angiotensin
7.	ARB	Angiotensin receptor blocker
8.	No.	Number
9.	BCS	Bio-pharmaceutical classification system
10.	BP	British Pharmacopoeia
11.	Cm	Centimetre
12.	Cps	Centipoise
13.	CR	Controlled release
14.	ER	Extended release
15.	et.al.	and others
16.	FTIR	Fourier Transform Infra-red Spectrophotometer
17.	G	Gram(s)
18.	g/mol	Gram/mole
19.	g/cc	Gram/cubic centimetre
20.	G.I.T	Gastrointestinal Tract
21.	Hr	Hour(s)
22.	HPMC	Hydroxy propyl methylcellulose
23.	IP	Indian Pharmacopoeia
24.	IR	Infra red

25.	JP	Japanese Pharmacopoeia
26.	KPa	Kilo Pascal
27.	log P	Partition coefficient
28.	mcg/µg	Microgram(s)
29.	Mg	Milligram(s)
30.	min(s)	Minutes
31.	ML	Millilitre(s)
32.	MPa	milli pascal
33.	NaOH	Sodium hydroxide
34.	Nm	Nanometer
35.	^{o}C	Degree centigrade
36.	%	Percentage
37.	q.s.	Quantity sufficient
38.	Rpm	Revolutions per minute
39.	SD	Standard deviation
40.	SR	Sustained release
41.	TDT	Tablet dissolution tester
42.	USP	United States Pharmacopoeia
43.	%	Percentage
44.	% w/v	Percentage weight/volume
45.	% w/w	Percentage weight/weight
46.	Cpr	Cumulative percentage drug release

INTRODUCTION

Tablets may be defined as solid pharmaceutical dosage forms containing drug substances with or without suitable diluents and prepared either by compression or molding methods. They have been in widespread use since the latter part of 19th century and their popularity continues. The term compressed tablet is believed to have been first used by 'John Wyeth and Philadelphinn'. During the same period molded tablets were introduced to be used as Hypodermic tablets for injections.

Tablets remain popular as a dosage form because of the advantages, afforded both to the manufacturer[eg. simplicity & economy of preparation, stability and convenience in packing, shipping, and dispensing] and the patient[eg .accuracy of dosage, compactness, poor stability, blendness of taste and ease of administration].

Although tablets are more frequently discoid in shape, they also may be round, oval, oblong, cylindrical or triangular. They may differ greatly in size and weight depending on the amount of drug substance present and the intended method of administration.

Tableting Formulations[1] :

In the tablet- pressing process, it is important that all ingredients be fairly dry, powdered or granular, somewhat uniform in practice size, and freely flowing. Mixed partical sieved powders can segregate during manufacturing operations due to different densities, which can result in tablets with poor drug or active pharmaceutical ingredients(API) content uniformity but granulation should prevent this. Content uniformity ensures that the same API dose is delivered with each tablet.

Some API may be as tabletted pure substances, But this is rarely the case; most formulations include excipients. Normally, an pharmacologically inactive ingredient(excipient) termed a binder is added it help hold the tablet together and give is strength. A wide variety of binders may be used, some common ones including lactose, dibasic calcium phosphate, sucrose, corn, maize, starch, microcrystalline cellulose and modified cellulose(for eg. hydroxypropyl methyl cellulose) ingredient is also needed to act as a disintegrate to aid tablet dispersion once swallowed, releasing the API for absorption. Some binders, such as starch and cellulose, are also excellent disintegrants.

Small amounts of lubricants are usually added as well. The most common of these is magnesium sterate; however, other commonly used tablet lubricants include stearic acid, stearin, hydrogenated oil, and sodium stearyl fumarate. These help the tablets once pressed, to be more easily ejected from the Die.

Types of Tablets:

Tablets are classified according to their route of administration or function. The following are the 4 main classification groups:

1. Tablets ingested orally

    a) Compressed tablets.

` b) Multiple compressed tablets.

    c) Multi layered tablets.

    d) Sustained action tablets.

    e) Enteric coated tablets.

    f) Sugar coated tablets.

    g) Film coated tablets.

    h) Chewable tablets.

2. **Tables used in the oral cavity, Buccal tablets**

a) Sublingual tablets .

b) Lozenge tablets and torches .

c) Dental cones.

3. Tablets administered by other routes

a) Implantation tablets .

b) vaginal tablets .

4. Tablets used to prepare solutions

a) Effervescent tablets, Molded tablets or tablet triturates(TT)

b) Dispersible tablets(DT)

c) Hypodermic tablets(HT)

Compressed tablets :

These tablets are uncoated and made by compression granules. These tablets are usually intended to provide rapid disintegration and drug release. These tablets contain water-soluble drugs, Which after swallowing get disintegrated in the stomach, and its drug contents are absorbed in the gastrointestinal tract and distribute in the whole body.

Multiple compressed tablets:

These tablets are prepared to separate physically or chemically incompatible ingredients or to produce repeated action prolonged action products. To avoid incompatibility, the ingredients of the formation except the incompatible materials are compressed into a tablet then incompatible substance along with necessary excipients are compressed in to a tablet.

Multi layered tablets:

These tablets contains of two or more layers of compressed successively in the same tablet. The color of each layer may be the same or different. The tablets having layers of different colors are known as "multicolored tablets".

Method of preparation of granules and tablets:

The manufacture of granulation of tablet compression may follow one or a combination of 3 established methods:

Direct compression:

In direct compression method the raw materials are size reduced and the required excipients are added and directly compressed. A few crystalline substances can be directly compressed into tablets. Tablets development of lower strength drugs may follow two processes either by traditional alcoholic or aqueous wet granulation technique or via the simple direct compression mode with marginally faster dissolution rates. Dosage strength with 1-10 mg per 100 or 150 mg tablet is considered suitable drug candidates for direct compression.

Wet granulation:

This is Most widely used ant the mist general methods of the tablet preparation. Its popularity is due to the greater possibility that granules will meet all physical requirements for the compression of good tablets. Most powders cannot be compresses directly into tablets because

the lack of proper characteristics of binding or together into a compact entity. The donor processes ordinarily lubricated and disintegrating properties. Wet granulation is the process in which the liquid is added to powder equipped with any type of agitation that will produce agglomeration or granules.

Dry granulation:

It is a valuable technique in situations where effective dose of a drug is too high for direct compression, and the drug is sensitive to heat, moisture, or both, which included wet granulation. This method involves the compaction of the components of a tablet formation by means of a tablet press or specially designed machinery, followed by milling and screening, prior to final compression into tablet. When the initial blend of powders forced is into dies of large capacity tablet press and is compacted by means of flat faced punches, the compacted masses are called "slugs" and the process is referred to as "slugging". On a large scale, "Compression granulation".

Excipients used in tablet formation:

Excipient means any component other than active pharmaceutical ingredient(s) intentionally added to the formation of a dosage form. Many guidelines exist to aid in selection of nontoxic excipients such as IIG(Inactive Ingredient Guide), GRAS(Generally Regarded as Safe). Handbook of pharmaceutical Excipients and other. While selecting excipients for any formulation following things should be considered wherever possible:

keep the excipients to a minimum in number, minimize the quantity of each excipient and multifunctional excipients may be given preference unifunctional excipients. Excipients play a crucial role in design of the delivery system, determining its quantity and performance. Excipients though usually regarded as nontoxic there are examples of known excipient induced toxicities which include renal failure and death from diethylene glycol, osmotic diarrhoea caused by ingested mannitol, hypersensitivity reactions from lanolin and cardiotoxicity induced by propylene glycol.

INTRODUCTION[2]

Oral drug delivery has been known for decades as the most widely utilized route of administration among all the routes that has been explored for the systemic delivery of drugs via various pharmaceutical products of different dosage form. Now-a-days most of the pharmaceutical scientists are involved in developing an ideal DDS. This ideal system should have advantage of single dose for whole duration of the treatment and it should deliver the drug directly at specific site. Scientists have succeeded to develop a system that can be as near to an ideal system and it encourages the scientists to develop controlled release system.

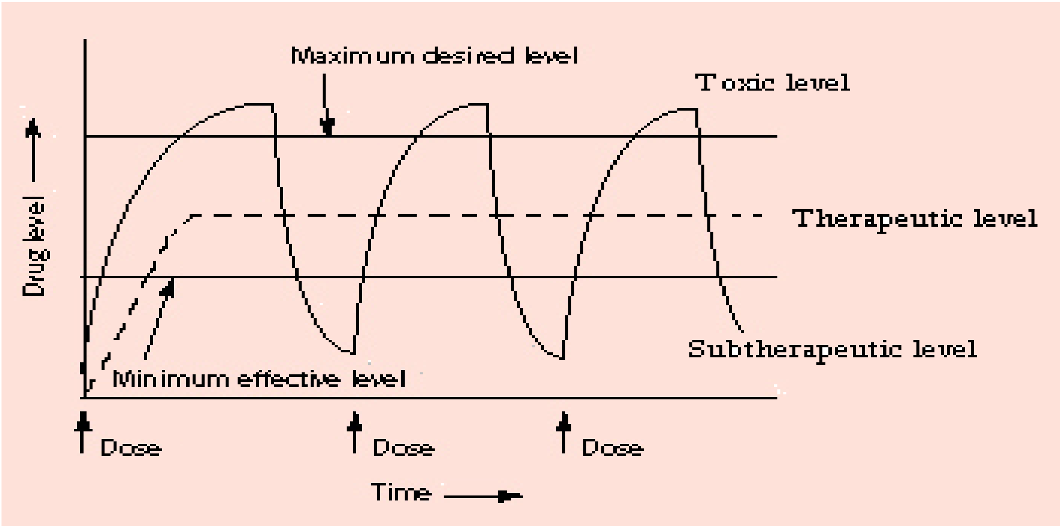

FIG:1 Plot Between Drug Release Level & Time

The design of oral sustain drug delivery system should be primarily aimed to achieve the more predictability and reproducibility to control the drug release, drug concentration in the target tissue and optimization of the therapeutic effect of a drug by controlling its release in the body with lower and less frequent dose.

Conventional drug therapy typically involves the periodic dosing of a therapeutic agent that has been formulated in a manner to ensure its stability, activity and bioavailability. For most of the drugs, conventional methods of formulation are quite effective. However some drugs are unstable and toxic and have a narrow therapeutic range, exhibit extreme solubility problems, require localization to a particular site in the body or require strict compliance or long-term use. In such cases a method of continuous administration of drug is desirable to maintain fixed plasma drug levels.The goal in designing sustained delivery systems is to reduce the frequency of the dosing or to increase effectiveness of the drug by localization at the site of action, reducing the dose required or providing uniform drug delivery. So, sustained release dosage form is a dosage form that release one or more drugs continuously in a predetermined pattern for a fixed period of time, either systemically or to a specified target organ. Sustained release dosage forms provide a better control of plasma drug levels, less dosage frequency, less side effect, increased efficacy and constant deliver

Classification modified release drug delivery system:

A.Delayed release.

B. Sustained release

Controlled release.

Extended release.

C)Site specific targeting

D)Receptor targeting

A) Delayed Release:These systems are those that use repetitive, intermittent dosing of a drug from one or more immediate release units incorporated into a single dosage form. Examples of delayed release systems include repeat action tablets and capsules and enteric-coated tablets where timed release is achieved by a barrier coating.

B) Sustained release: During the last two decades there has been remarkable increase in interest in sustained release drug delivery system. This has been due to various factor such as the prohibitive cost of developing new drug entities, expiration of existing international patents, discovery of new polymeric materials suitable for prolonging the drug release, and the improvement in therapeutic efficiency and safety achieved by these delivery systems. Now-a-days the technology of sustained release is also being applied to veterinary products. These systems also provide a slow release of drug over an extended period of time and also can provide some control, whether this be of a temporal or spatial nature, or both, of drug release in the body, or in other words, the system is successful at maintaining constant drug levels in the target tissue or cells.

Controlled release: These system include any pharmaceutical dosage forms that achieves slow release of drug over an extended period of time.

2) Extended Release:The system include any pharmaceutical dosage forms that release the drug slower than normal manner at predetermined rate & necessarily reduce the dosage frequency by two folds.

C) Site specific targeting: These system refers, targeting a drug directly to a certain biological location. In this case the target is adjacent to or in the diseased organ or tissue.

D) Receptor targeting:These system refer, targeting of a drug directly to a certain biological location. In this case the target is the particular receptor for a drug within an organ or tissue. Site specific targeting and receptor targeting systems satisfy the special aspect of drug delivery and are also considered to be sustained drug delivery systems.

Potential advantages and disadvantages of sustained release dosage forms

Advantages:

- Avoid patient compliance problems.
- Minimize or eliminate local side effects.
- Minimize or eliminate systemic side effects.
- Obtain less potentiation or reduction in drug activity with chronic use.
- Minimize drug accumulation with chronic dosing.
- Improve efficiency in treatment.
- Cure or control condition more promptly.
- Reduction in fluctuation of blood drug level.
- Improve bioavailability of some drugs.
- Make use of special effects, e.g. sustained-release aspirin for morning relief of arthritis by dosing before bedtime.
- SR drug delivery system aims at optimized therapy constant blood levels.

- Constant blood levels achieved with desired effect and this effect is maintained for an intended period of time.

- Drugs susceptible to enzymatic inactivation or by bacterial decomposition can be protected by encapsulation in polymer system suitable for SR.

- For drugs having specific window for absorption increased bioavailability can be attained by localizing the SR in that particular region of the GIT.

- Economy

DISADVANTAGES OF SUSTAINED RELEASE DOSAGE FORMS:

- They are costly. Increased variability among dosage units

- Dose dumping

Challenges: **Dose dumping:**Dose dumping is a phenomenon where by relatively large quantities of drug in a sustained release formulation is rapidly released, introducing potential toxic quantities of the drug into the systemic circulation. Dose dumping can lead to facialities in case of potent drug, which have a narrow therapeutic index.

eg; Phenobarbital.

Limited choice of selecting desired dose in the unit. In conventional dosage forms, dose adjustments are much simpler e.g. tablet can be divided into two fractions. In case of sustained release dosage forms, this appears to be much more complicated. Sustained release property may get lost, if dosage form is fractured.

Poor *In- Vitro In - Vivo* correlation:

In sustained release dosage form, the rate of drug release is deliberately reduced to achieve drug release possibly over a large region of gastrointestinal tract. Here so called

'*Absorptionwindow'* becomes important and may give rise to un-satisfactory drug absorption in in-vivo despite excellent in in-vitro release**.**

Patient variation

The time period required for absorption of drug, released from the dosage form may vary among individuals. Co-administration of other drugs, presence or absence of food and residence time in gastrointestinal tract is different among patients. This also gives rise to variation in clinical response among the patient.

Criteria to be met by drug proposed to be formulated in sustained release dosage forms.

a) Desirable half-life.

b) High therapeutic index

c) Small dose

d) Desirable absorption and solubility characteristics.

e) Desirable absorption window.

f) First pass clearance

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Floating drug delivery system

1. Single unit floating dosage form

a. Non-effervescent systems: [5,11]

The most commonly used excipients in non-effervescent FDDS are gel forming or highly swellable cellulose type hydrocolloids, polysaccharides and matrix forming polymers such as polycarbonate, polyacrylate, polymethacrylate and polystyrene., which swells in contact with gastric fluids after oral administration and maintains a relatve integrity of shape, bulk density of less than unity. The air entrapped by the swollen polymer confers buoyancy to these dosage forms.

i. Colloidal gel barrier system: [11]This system incorporates a high level (20-75%w/w) of one or more gel-forming, highly swellable, cellulose type hydrocolloids (e.g. Hydroxy ethyl cellulose, hydroxy propyl cellulose, hydroxy propyl methyl cellulose , sodium carboxymethyl cellulose) polysaccharides and matrix forming polymers such as polycarbophil, polyacrylates and polystyrene, incorporated either in tablets or in capsules. When coming in contact with gastric fluid, the hydrocolloid in the system hydrates and form colloidal gel barrier around its surface. This gel-barrier control the rate of fluid penetration into the device and consequent release of the drug. As the exterior surface of the dosage form goes into the solution, the gel layer is maintained by the adjacent hydrocolloid layer becoming hydrated. The air trapped in by the swollen polymer maintains a density less than unity and confers buoyancy to these dosage forms.

The HBS must comply with 3 major criteria:

1) It must have sufficient structure to form a cohesive gel barrier.

2) It must maintain an overall specific density lower than that of gastric contents.

3) It should dissolve slowly enough to serve as a reservoir for the delivery system.

A bilayer tablet can also be prepared to contain one immediate-release and sustained release layer. Immediate-release layer delivers the initial dose, whereas SR layer absorbs gastric fluid and forms a colloidal gel barrier on its surface. This results in a system with bulk density lesser than that of the gastric fluid, and allows it to remain buoyant in stomach for an extended period of time.

ii. Microporouscompartmentsystem:

This technology is based on the encapsulation of a drug reservoir inside a microporous compartment with apertures along its top and bottom walls. The peripheral wall of the drug reservoir compartment is completely sealed to prevent any direct contact of gastric mucosal surface with the un-dissolved drug. In stomach, the floatation chamber containing entrapped air causes the delivery system to float over the apertures, dissolves the drug and carries the dissolved drug for continuous transport across the intestine for absorption.

b. Effervescent systems:[11]

A drug delivery system can be made to float in the stomach by incorporating a floating chamber, which may be filled with vaccum, air or inert gas. The gas in the floating chamber can be introduced either by the volatilization of an organic solvent or by the effervescent reaction between organic acids and bicarbonate salts.

i. Volatile liquid containing systems:[11]

The GRT of a drug delivery system can be sustained by incorporating an inflatable chamber which contains a liquid e.g. ether, cyclopentane that gasifies at body temperature to cause the inflatation of the chamber in the stomach. These devices are osmotically controlled floating systems containing a hollow deformable unit that can convert from a collapsed to an expanded position and returns to collapsed position after an extended period. The deformable system consists of two chambers separated by an impermeable, pressure-responsive, movable bladder. The first chamber contains the volatile liquid. The device inflates and the drug is continuously released from the reservoir into the gastric fluid. The device may also consists of a bioerodible plug made up of PVA, polyethylene etc. that gradually dissolves causing the inflatable chamber to release gas and collapse after a predetermined time to permit spontaneous ejection of the inflatable system from the stomach.

ii. Gas-generating systems : [6,11]

These buoyant systems use matrices prepared with swellable polymers like HPMC, polysaccharides like chitosan, effervescent components like sodium bicarbonate, citric acid, tartaric acid, Di-sodium glycine carbonate, citroglycine etc. The optimal stoichiometric ratio of citric acid and sodium bicarbonate for gas generation is reported to be 0.76:1. Effervescent reaction between bicarbonate salts and citric acid/tartaric acid liberates CO^2,which gets entrapped in the gellified hydrocolloid layer of the system, thus decreasing its specific gravity and making it to float over chyme. These tablets may be either single layered wherein the carbondioxide generating components are intimately mixed within the tablet matrix, or they may be bilayered in which the gas generating components are compressed in hydrocolloid containing layer and the drug in other layer formulated for a SR effect.

2. Multiple unit floating dosage form

a. Non-effervescent system

i. Alginate beads: [11] Spherical beads of approximately 2.5mm in diameter can be prepared by dropping a sodium alginate solution into aqueous solution of calcium alginate. The beads are then separated, snap frozen in liquid nitrogen and freeze-dried at 40^0c for 24 hours, leading to the formation of a porous system, which can maintain a floating force for 12 hours.

ii. **Hollow microspheres:** [6] Hollow microspheres are considered as one of the most promising buoyant systems as they possess the unique advantages of multiple unit systems as well as better floating properties, because of the central hollow space inside the microsphere. The general techniques involved in their preparation include simple solvent evaporation and solvent diffusion and evaporation. Polymers such as polycarbonate, eudragit S and cellulose acetate are used in the preparation of hollow microspheres and the drug release can be modified by optimizing the amount of polymer-plasticizer ratio. Hollow microspheres floated with drug in their outer polymer shelf can also be prepared by a novel emulsion solvent-diffusion method. The ethanol/dichloromethane solution of the drug and an enteric acrylic polymer was poured into an agitated solution of poly vinyl alcohol that was thermally controlled at 40^0C. The gas phase is generated in the dispersed polymer droplet by the evaporation of dichloromethane formed an internal cavity in the microsphere of the polymer with drug. The microballoon floated continuously over the surface of an acidic dissolution media containing surfactant for more than 12 hours.

b. Gas-generating systems: [11] Multi unit types of floating pills, which generate CO_2 have also been developed. The system consists of a SR pill as seed, surrounded by double layers. The inner layer is an effervescent layer containing sodium bicarbonate and tartaric acid. When the system is immersed in buffer solution at 37^0**C** swollen pills, like balloons are formed having density less than 1g/ml. This occurs due to CO_2 neutralization of the inner effervescent layer with the diffusion of water through the outer swellable membrane layer. These kinds of systems float completely within 10min and remain floating over extended periods of 5-6 hours.

c. Ion-exchange resin system: [5]The system consisted of resin beads, which were loaded with the bicarbonate and a negatively charged drug that was bound to the resin. The resultant beads were then encapsulated in a semipermeable membrane to overcome rapid loss of CO_2. Upon arrival in the acidic environment of stomach, an exchange of chloride and bicarbonate ions took place. As a result of this reaction, carbondioxide was released and trapped in the membrane, thereby carrying beads towards the top of gastric contents and producing a floating layer of resin beads.

Bio/Mucoadhesive systems[2]

Bioadhesive drug delivery systems (BDDS) are useful as a delivery device within the lumen to enhance drug absorption in a site-specific manner. This approach involves the use of bioadhesive polymers, which can adhere to the epithelial surface in the stomach. Gastric mucoadhesion does not tend to be strong enough to impart the dosage forms the ability to resist the strong propulsion forces of the stomach wall. The continuous production of mucous that is lost through peristalitic contractions and the dilution of the stomach contents also seem to limit the potential of mucoadhesion as a gastroretentive force. Some of the most promising excipients that have been used commonly in these systems include polycarbophil, carbopol, lectins, chitosan and gliadin etc. The adhesion of the polymers with the mucous membrane may be mediated by hydration, bonding or receptor mediated.

Swelling systems[3]

Swelling systems are also referred to as plug type systems. The presence of polymers in the systems promotes their swelling to a size that prevents their passage through pyloric sphincter resulting in prolonged GRT. However, a balance between the rate and extent of swelling and the rate of erosion of the polymer is crucial to achieve optimum benefits and to avoid unwanted side effect

High density system[12]

This approach involves formulation of dosage forms with the density that must exceed density of normal stomach content (1.004g/cm3). These formulations are prepared by coating drug on a heavy core or mixed with heavy inert materials such as iron powder, zinc oxide, titanium dioxide or barium sulphate. These resultant pellets can be coated with diffusion controlled membrane. These systems with a density of about 3g/cm3 are retained in the rugae of the stomach and are capable of withstanding its peristalitic movements. 2.6-2.8g/cm^3 acts as a threshold density after which such systems can be retained in the lower part of the stomach.

Expansive gastroretentive dosage form[12]

This is a class of gastroretentive systems capable of expanding in stomach. The expanded structure is trapped in stomach for prolonged period leading to sustained drug release and subsequent controlled absorption in stomach and intestine. These systems are administered perorally in the form of capsule bearing the dosage form in folded and compact configuration. When exposed to gastric environment capsule shell breaks and the dosage form attains its expanded structure, which is retained in stomach for longer time.

Raft forming systems[3, 4]

Raft forming systems have received much attention for the delivery of antacids and drug delivery for gastrointestinal infections and other disorders. The mechanism involved in the raft formation includes the formation of a viscous cohesive gel in contact with gastric fluids, wherein each portion of the liquid swells forming a continuous layer called a raft. This raft floats on gastric fluids because of the low bulk density created by the formation of CO_2. Usually, the system contains a gel forming agents and alkaline bicarbonates or carbonates responsible for the formation of CO2 to make the system less dense and able to float on the gastric fluids. This floating rafts impedes the reflux of acids and food by acting as a physical barrier. The raft has a pH value higher than that of the stomach contents so that in the event of gastric reflux, the wall of the esophagus is not subjected to irritation by HCl.

Suitable drug candidates for gastroretention.[4]

In general, appropriate candidates for CR-GRDF are molecules that have poor colonic absorption but are characterized by better absorption properties at the upper parts of the GIT:

- Narrow absorption window in GI tract, e.g. Riboflavin and Levodopa.
- Primarily absorbed from stomach and upper part of GI tract e.g. Calcium. supplements, Chlorodiazepoxide and Cinnarazine.
- Drugs that act locally in the stomach e.g. Antacids and Misoprostol.
- Drugs that degrade in the colon e.g. Ranitidine HCl and Metronidazole.
- Drugs that disturb normal colonic bacteria, e.g. Amoxicillin trihydrate.

Factors affecting floating drug delivery system[3,5,7]

1. Density of dosage form: Dosage forms having a density lower than that of gastric fluid experience floating behavior and hence gastric retention. Density $<1.0g/cm^3$ is required to exhibit floating property.

2. Size of dosage form: The size of the dosage form is another factor that influences gastric retention .The mean gastric residence times of non-floating dosage forms are highly variable and greatly dependent on their size, which may be small, medium and large units. In fed conditions, the smaller units get emptied from the stomach during the digestive phase and the larger units during the house keeping waves. In most cases, the larger the size of the dosage form the greater will be the gastric retention time because the larger size would not allow the dosage form to quickly pass through the pyloric sphincter into the intestine. Dosage form units with a diameter more than 7.5mm are reported to increase GRT compared with those with diameter of 9.9mm.

3. Food intake and nature of food: Food intake, the nature of the food, caloric content and frequency of feeding has a profound effect on the gastric retention of dosage forms. The presence or absence of food in the stomach influences the GRT of the dosage forms. Usually, the presence of food increases the GRT of the dosage form and increases drug absorption by allowing it to stay at the absorption site for a longer time. Usually fats tend to form an oily layer on the other gastric contents. As such, fatty substances are emptied later than other. Also, increased acidity and osmolality slow down gastric emptying.

4. Stress: stress appears to cause an increase in gastric emptying rate, while depression slows it down.

5. **Shape:** Tetrahedron and ring-shaped devices with a flexural modulus of 48 and 22.5 kilo pounds per square inch (KSI) are reported to exhibit a better GRT and 90%-100% retention at 24hour compared with other shapes.

6. **Concomitant drug administration:** Anticholinergics like atropine and propantheline, opiates like codeine and prokinetic agents like metoclopramide and cisapride affect the FDDS.

7. Sex: women and elderly have a slower gastric emptying rate than men and young people respectively.

8. Posture: In a comparative study in humans by Gansbeke et al; the floating and non-floating systems behaved differently. In the upright position, the floating systems floated to the top of the gastric contents and remained for a longer time, showing prolonged GRT. But the non-floating units settled to the lower part of the stomach and underwent faster emptying as a result of peristaltic contractions and the floating units remained away from the pylorus. However, in supine position, the floating units are emptied faster than non-floating units of similar size. A study by Mojaverian et al., showed that effect of posture on GRT found no significant difference in mean GRT for individuals in upright, ambulatory and supine state.

9. **Shape:** Tetrahedron and ring-shaped devices with a flexural modulus of 48 and 22.5 kilo pounds per square inch (KSI) are reported to exhibit a better GRT and 90%-100% retention at 24hour compared with other shapes .

10. **Concomitant drug administration:** Anticholinergics like Atropine and Propantheline, opiates like Codeine and prokinetic agents like Metoclopramide and Cisapride affect the FDDS

11. **Biological factors:** Diabetes and crohn's disease also affect the FDDS.

Advantages of gastro retentive drug delivery system[4,7]

1. Enhanced bioavailability: The bioavailability of Riboflavin CR-GRDF is significantly enhanced in comparison to the administration of non-GRDF CR polymeric formulation.

2. Enhanced first-pass biotransformation: In a similar fashion to the increased efficacy of active transporters exhibiting capacity limited activity, the pre-systemic metabolism of the tested compound may be considerably increased when the drug is presented to the metabolic enymes (Cytochrome P450, in particular CYP3A4) in a sustained manner, rather than by a bolus input.

3. Sustained drug delivery/ reduced frequency of dosing: For drug with relatively short biological half-life, sustained and slow input from CR-GRDF may result in a flip-flop pharmacokinetics and enable reduced dosing frequency. This feature is associated with improved patient compliance and thereby improves therapy.

4. Targeted therapy for local ailments in the upper GIT: The prolonged and sustained administration of the drug from GRDF to the stomach may be advantageous for local therapy in the stomach and small intestine as in the case of H.pylori induced peptic ulcer.

5. Reduced fluctuations of drug concentration: Continuous input of the drug following CR-GRDF administration produces blood drug concentrations within a narrow range compared to the immediate release dosage forms. Thus, fluctuations in drug effects are minimized and concentration dependent adverse effects that are associated with peak concentrations can be prevented. This feature is of special importance for drugs with a narrow therapeutic index.

6. Extended time over critical (effective) concentration: The sustained mode of administration enables extension of the time over a critical concentration and thus enhances the pharmacological effects and improves the clinical outcomes.

7. Site specific drug delivery: A floating dosage form is a feasible approach for drugs which have limited absorption sites in upper small intestine

8. Minimized adverse activity at the colon: Retention of the drug in the GRDF at the stomach minimizes the amount of drug that reaches the colon. Thus, undesirable activities of drug in the colon may be prevented as in the case of β-lactam antibiotics.

9. Administration of a prolonged release floating dosage form tablets or capsules will result in dissolution of the drug in gastric fluid. After emptying of the stomach contents, the dissolved drug available is for absorption in the small intestine. It is therefore expected that a drug will be fully absorbed from the floating dosage form if it remains in solution form even at alkaline pH of the intestine.

10. When there is vigorous intestinal movement and a short transit time as might occur in certain type of diarrhea, poor absorption is expected under such circumstances and it may be advantageous to keep the drug in floating condition in stomach to get a relatively better response.

11. Many drugs categorized as once-a-day delivery have been demonstrated to have suboptimal absorption due to dependence on the transit time of the dosage form making traditional extended release development challenging. Therefore, a system designed for longer gastric retention will extend the time within which drug absorption can occur in small intestine.

Limitations of Floating drug delivery system[11,12]

1. They require a sufficiently high level of fluids in the stomach, for enabling the system to float and to work efficiently. This limitation can be over whelmed by coating the dosage form with bioadhesive polymer or alternatively by prescribing the dosage form to be taken up with a glass full of water (200-250ml).

2. FDDS are not suitable candidates for drugs with stability or solubility problem in stomach.

3. Some drugs like nifedipine, which is well absorbed along the entire GI tract and undergoes extensive first pass metabolism may not be suitable for FDDS as the slow gastric emptying limits the systemic bioavailability.

4. Drugs with irritant effect on gastric mucosa also limit the applicability of FDDS.

5. In case of bioadhesive systems, which form electrostatic and hydrogen bonds with the mucus, the acidic environment and the thick mucus prevent the bond formation at the mucus polymer interface. High turnover rate of the mucus may further aggravate the problem**.**

6. For swellable systems, the maintenance of their size larger than the aperture of resting pylorus for required period of time is the major rate limiting factor.

7. Above all, any dosage form designed to stay in stomach during the fasting state should be capable of resisting the house keeper waves of phase-III contractions of MMC.

Applications of floating drug delivery systems[6,8]

1. Sustained drug delivery: HBS systems can remain in the stomach for long periods and hence can release the drug over a prolonged period of time. The problem of short gastric residence time encountered with an oral CR formulation hence can be overcome with these systems. These systems have a bulk density of less than1 as a result of which they can float on the gastric contents. These systems are relatively large in size and passing from the pyloric opening is prohibited. Recently sustained release floating capsules of nicardipine hydrochloride were developed and were evaluated in vivo. The formulation compared with commercially available MICARD capsules using rabbits. Plasma concentration time curves showed a longer duration for administration (16hours) in the sustained release floating capsules as compared with conventional MICARD capsules (8hours).

2. **Site-specific drug delivery**: These systems are particularly advantageous for drugs that are specifically absorbed from stomach or the proximal part of the small intestine e.g. Riboflavin and Furosemide. A bilayer-floating capsule was developed for local delivery of Misoprostol, which is a synthetic analog of prostaglandin E1 used as a protectant of gastric ulcers caused by administration of NSAIDs. By targeting slow delivery of misoprostol to the stomach, desired therapeutic levels could be achieved and drug waste could be reduced.

3. Absorption enhancement: Drugs that have poor bioavailability because of site-specific absorption from the upper part of the gastrointestinal tract are potential candidates to be formulated as floating drug delivery systems, there by maximizing their absorption. A significant increase in the bioavailability of floating dosage forms (42.9%) could be achieved as compared with commercially available LASIX tablets (33.4%) and enteric coated LASIX-long product (29.5%).

4. Medopar HBS – containing L-dopa and benserazide-here drug was released and absorbed over a period of 6-8 hour and maintain substantial plasma concentration in Parkinson's patients.

5. Cytotech- containing misoprostol, a synthetic prostaglandin-E1 analog, for prevention of gastric ulcers caused by NSAID´s. As it provides high concentration of drug within gastric mucosa, it is used to eradicate pylori.

6. 5-Flurouracil has been successfully evaluated in patients with stomach neoplasm.

7. Developing HBS dosage form for Tacrine provides a better delivery system and reduces its GI side effects in Alzheimer's patients.

5 Hypertension:

Hypertension (HTN) or high blood pressure, sometimes called arterial hypertension, is a chronic medical condition in which the blood pressure in the arteries is elevated. Blood pressure involves two measurements, systolic and diastolic, which depend on whether the heart muscle is contracting (systole) or relaxed between beats (diastole). Normal blood pressure at rest is within the range of 100-140mmHg systolic (top reading) and 60-90mmHg diastolic (bottom reading). High blood pressure is said to be present if it is persistently at or above 140/90 mmHg.

Hypertension is classified as either primary (essential) hypertension or secondary hypertension; about 90–95% of cases are categorized as "primary hypertension" which means high blood pressure with no obvious underlying medical cause. The remaining 5–10% of cases (secondary hypertension) are caused by other conditions that affect the kidneys, arteries, heart or endocrine system.

Table no 1: Classification of hypertension

Classification	Systolic pressure		Diastolic pressure	
	mm Hg	KPa	MmHg	KPa
Normal	90–119	12–15.9	60–79	8.0–10.5
Prehypertension	120–139	16.0–18.5	80–89	10.7–11.9
Stage 1 hypertension	140–159	18.7–21.2	90–99	12.0–13.2
Stage 2 hypertension	≥160	≥21.3	≥100	≥13.3
Isoloated systolic hypertension	≥140	≥18.7	<90	<12.0

Signs and symptoms:

Hypertension is rarely accompanied by any symptoms, and its identification is usually through screening, or when seeking healthcare for an unrelated problem. A proportion of people with high blood pressure reports headaches (particularly at the back of the head and in the morning), as well as lightheadedness, vertigo, tinnitus (buzzing or hissing in the ears), altered vision or fainting episodes.

On physical examination, hypertension may be suspected on the basis of the presence of hypertensive retinopathy detected by examination of the optic fundus found in the back of the eye using ophthalmoscopy.

Secondary hypertension:

Some additional signs and symptoms may suggest secondary hypertension, i.e. hypertension due to an identifiable cause such as kidney diseases or endocrine diseases. For example, truncal obesity, glucose intolerance, moon facies, a "buffalo hump" and purple striae suggest Cushing's syndrome.

Hypertensive crises:

Severely elevated blood pressure (equal to or greater than a systolic 180 or diastolic of 110 sometime termed malignant or accelerated hypertension) is referred to as a "hypertensive crisis", as blood pressures above these levels are known to confer a high risk of complications. People with blood pressures in this range may have no symptoms, but are more likely to report headaches (22% of cases) and dizziness than the general population. Other symptoms accompanying a hypertensive crisis may include visual deterioration or breathlessness due to heart failure or a general feeling of malaise due to renal failure**.**

In pregnancy

Hypertension occurs in approximately 8-10% of pregnancies. Most women with hypertension in pregnancy have pre-existing primary hypertension, but high blood pressure in pregnancy may be the first sign of pre-eclampsia, a serious condition of the second half of pregnancy and puerperium. Pre-eclampsia is characterised by increased blood pressure and the presence of protein in the urine.

In infants and children:

Failure to thrive, seizures, irritability, lack of energy, and difficulty breathing can be associated with hypertension in neonates and young infants. In older infants and children, hypertension can cause headache, unexplained irritability, fatigue, failure to thrive, blurred vision, nosebleeds, and facial paralysis.

Complications:

Hypertension is the most important preventable risk factor for premature death worldwide. It increases the risk of ischemic heart disease strokes, peripheral vascular disease, and other cardiovascular diseases, including heart failure, aortic aneurysms, diffuse atherosclerosis, and pulmonary. Hypertension is also a risk factor for cognitive impairment and dementia, and chronic kidney disease. Other complications include:

- Hyperten sive retinopathy.

- Hypertensive nephropathy.

Cause:

Primary hypertension

Primary (essential) hypertension is the most common form of hypertension, accounting for 90–95% of all cases of hypertension. Hypertension results from a complex interaction of genes and environmental factors. Numerous common genes with small effects on blood pressure have been identified as well as some rare genes with large effects on blood pressure but the genetic basis of hypertension is still poorly understood. Several environmental factors influence blood pressure. Lifestyle factors that lower blood pressure, include reduced dietary salt intake, increased consumption of fruits and low fat products (Dietary Approaches to Stop Hypertension (DASH diet)), exercise, weight loss and reduced alcohol intake.

Secondary hypertension

Secondary hypertension results from an identifiable cause. Renal disease is the most common secondary cause of hypertension.

Hypertension can also be caused by endocrine conditions, such as Cushing's syndrome, hyperthyroidism, hypothyroidism, acromegaly, Conn'ssyndrome or hyperaldosteronism hyperparathyroidism and pheochromocytoma.

Pathophysiology:

In most people with established essential (primary) hypertension, increased resistance to blood flow (total peripheral resistance) accounting for the high pressure while cardiac outpu tremains normal.

Pulse pressure (the difference between systolic and diastolic blood pressure) is frequently increased in older people with hypertension. This can mean that systolic pressure is abnormally high, but diastolic pressure may be normal or low a condition termed isolated systolic hypertension. The high pulse pressure in elderly people with hypertension or isolated systolic hypertension is explained by increased arterial stiffness, which typically accompanies aging and may be exacerbated by high blood pressure.

Many mechanisms have been proposed to account for the rise in peripheral resistance in hypertension. Most evidence implicates either:

- Disturbances in renal salt and water handling, particularly abnormalities in the intrarenal renin-angiotensin system and/or

- Abnormalities of the sympathetic nervous system

These mechanisms are not mutually exclusive and it is likely that both contribute to some extent in most cases of essential hypertension. It has also been suggested that dysfunction and vascular inflammation may also contribute to increased peripheral resistance and vascular damage in hypertension.

Diagnosis

Table no 2: Typical tests performed in hypertension

Renal	Microscopic urinalysis, proteinuria, serum BUN (blood urea nitrogen) and/or creatinine
Endocrine	Serum sodium, potassium, calcium, TSH (thyroid-stimulating hormone).
Metabolic	Fasting blood glucose, total cholesterol, HDL and LDL cholesterol, triglycerides
Other	Hematocrit, electrocardiogram, and chest radiograph

Prevention:

For the primary prevention of hypertension:

- Maintain normal body weight for adults (e.g. body mass index 20–25 kg/m^2).
- Reduce dietary sodium intake to <100 mmol/ day (<6 g of sodium chloride or <2.4 g of sodium per day).
- Engage in regular aerobic physical activity such as brisk walking (≥30 min per day, most days of the week).
- Limit alcohol consumption to not more than 3 units/day in men and not more than 2 units/day in women.
- Consume a diet rich in fruit and vegetables (e.g. at least five portions per day).

Management:

Lifestyle modifications

The first line of treatment for hypertension is identical to the recommended preventative lifestyle changes and includes: dietary changes physical exercise, and weight loss.

Medications

Several classes of medications, collectively referred to as antihypertensive drugs, are currently available for treating hypertension.

(The best first line agent is disputed. The Cochranes collaboration, World Health Organization and the United States guidelines supports low dose thiazide-based diuretic as first line treatment.)

AIM AND OBJECTIVES

Losartan Potassium is an angiotensin-receptor blocker (ARB) that may be used alone or with other agents to treat hypertension. The aim of study is to formulate and evaluate of sustained release floating tablet of losartan potassium .To study the effect of polymers on the release of Losartan potassium, different polymers are used to attain floating sustained drug release and give maximum therapeutic effect for prolonged period of time when taken orally, to design a formulation of solid dosage of Losartan potassium tablets with better stability of high product quality.

The objectives of the present work include:

1. Drug-polymer interaction studies.
2. Preparation of Losartan Potassium sustained release floating tablets using different polymers by direct compression technique.
3. Evaluation of floating tablets for pre and post compression parameters.
4. Physical parameters like hardness, friability, weight variation, drug content uniformity.
5. *In-Vitro* evaluation of sustained release tablets for the release characteristics.
6. To carry out stability studies for selected formulation as per ICH guidelines.

PLAN OF WORK

The plan of the research work has been scheduled as:

1.API and excipients characterization to prepare solid oral dosage form of losartan potassium.

2.preformulation studies:

compatability studies.

solubility.

Angle of repose.

Bulk density.

Tapped density.

Compressibility index.

Hausner ratio.

3.Development of sustained released floating Tablets by direct compression method.

4.Evaluation of the formulated tablets for their physio chemical characteristics such as:

Hardness.

Thickness.

Friability.

weight variation.

Floating log time.

Content uniformity.

5.*In- vitro* dissolution study of the prepared tablets of Losartan potassium.

6.stability studies.

DRUG PROFILE

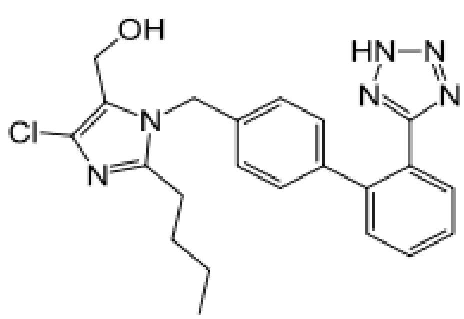
Description:

Losartan is an angiotensin-receptor blocker (ARB) that may be used alone or with other agents to treat hypertension.

Categories:

- Antihypertensive Agents.
- Angiotensin II Receptor Antagonists.
- Antiarrhythmic Agents.
- Angiotensin II Type 1 Receptor Blockers.
- Anti-Arrhythmia Agents.

Structure of Losartan Potassium



Molecular Formula: $C_{22}H_{23}ClN_6O$•K ½$C_4H_40_4$

Chemical Name: 2 - Butyl - 4 - chloro - 1 - [[2′ - (1H - tetrazol - 5 - yl)[1,1′ - biphenyl] - 4 - yl] - methyl] - 1H - imidazole - 5 - methanol monopotassium salt

State: solid

Melting point: 183.5-184.5 ^{o}C

Experimental properties :

Table no:3

PROPERTY	VALUE
WATER SOLUBILITY	0.82mg/L
Log p	6.1

Molecular weight: Average: 422.911g/mol

Pharmacology:

Indications

May be used as a first line agent to treat uncomplicated hypertension, isolated systolic hypertension and left ventricular hypertrophy. May be used as a first line agent to delay progression of diabetic nephropathy. Losartan may be also used as a second line agent in the treatment of congestive heart failure, systolic dysfunction, myocardial infarction and coronary artery disease in those intolerant of ACE inhibitors.

Pharmacodynamics

Losartan is the first of a class of antihypertensive agents called angiotensin II receptor blockers (ARBs). Losartan and its longer acting active metabolite, E-3174, are specific and selective type-1 angiotensin II receptor (AT1) antagonists which block the blood pressure increasing effects angiotensin II via the renin-angiotensin-aldosterone system (RAAS). RAAS is a homeostatic mechanism for regulating hemodynamics, water and electrolyte balance. During sympathetic stimulation or when renal blood pressure or blood flow is reduced, renin is released from granular cells of the juxtaglomerular apparatus in the kidneys. Renin cleaves circulating angiotensinogen to angiotensin I, which is cleaved by angiotensin converting enzyme (ACE) to angiotensin II. Angiotensin II increases blood pressure by increasing total peripheral resistance, increasing sodium and water reabsorption in the kidneys via aldosterone secretion, and altering cardiovascular structure. Angiotensin II binds to two receptors: AT1 and type-2 angiotensin II receptor (AT2). AT1 is a G-protein coupled receptor (GPCR) that mediates the vasoconstrictive and aldosterone-secreting effects of angiotensin II. Studies performed in recent years suggest that AT2 antagonizes AT1-mediated effects and directly affects long-term blood pressure control by inducing vasorelaxation and increasing urinary sodium excretion. Angiotensin receptor blockers (ARBs) are non-peptide competitive inhibitors of AT1. ARBs block the ability of angiotensin II to stimulate pressor and cell proliferative effects. Unlike ACE inhibitors, ARBs do not affect bradykinin-induced vasodilation. The overall effect of ARBs is a decrease in blood pressure.

Mechanism of action:

Losartan competitively inhibits the binding of angiotensin II to AT1 in many tissues including vascular smooth muscle and the adrenal glands. Losartan is metabolized to its active metabolite, E-3174, which is 10 to 40 times more potent than losartan and acts as a non-competitive AT1 antagonist. Inhibition of angiotensin II binding to AT1 inhibits its AT1-mediated vasoconstrictive and aldosterone-secreting effects and results in decreased vascular resistance and blood pressure. Losartan is 1,000 times more selective for AT1 than AT2. Inhibition of aldosterone secretion may increase sodium and water excretion while decreasing potassium excretion. Losartan is effective for reducing blood pressure and may be used to treat essential hypertension, left ventricular hypertrophy and diabetic nephropathy.

Absorption:

Well absorbed, the systemic bioavailability of losartan is approximately 33%.

Volume of distribution:

- 34 L [losartan]
- 12 L [active metabolite]

Protien binding: 99.7%, primarily to albumin.

Metabolism:

Hepatic: Losartan is metabolized to a 5-carboxylic acid derivative (E-3174) via an aldehyde intermediate (E-3179) primarily by cytochrome P450 (CYP) 2C9 and CYP3A4. E-3174 is an active metabolite with 10- to 40-fold higher potency than its parent compound, losartan. Approxiamtely 14% of losartan is converted to E-3174; however, the AUC of E-3174 was found to be 4- to 8-fold higher than losartan and E-3174 is considered the main contributor to the pharmacologic effects of this medication.

Route of elimination:

After single doses of losartan administered orally, about 4% of the dose is excreted unchanged in the urine and about 6% is excreted in urine as active metabolite. Biliary excretion contributes to the elimination of losartan and its metabolites.

Half life:

The terminal $t_{1/2}$ of losartan is 2 hours and that of E-3174 is 6-9 hours.

Clearence:

600 ml/min [Healthy volunteers after IV administration]

Renal cl=56 ± 23 ml/min [Hypertensive adults given 50 mg once daily for 7 days]

Renal cl=53 ± 33 ml/min [Hypertensive children (6-16 years old) given 0.7 mg/kg once daily for 7 days]

Toxicity: [14]

Hypotension and tachycardia; Bradycardia could occur from parasympathetic (vagal) stimulation, LD_{50}= 1000 mg/kg (orally in rat).

EXCIPIENT PROFILE

MICROCRYSTALLINE CELLULOSE[35]

Nonproprietary NamesBP:

JP: Microcrystalline cellulose.

Microcrystalline cellulose.

PhEur: Cellulosum microcsristallinum.

USPNF: Microcrystalline cellulose.

Synonyms:

BP:Microcrystalline cellulose.

JP: Microcrystalline cellulose.

PhEur: Cellulosum microcristallinum.

USPNF: Microcrystalline cellulose.

Functional Category:

Adsorbent; suspending agent; tablet and capsule diluent; tablet disintegrant.

Description:

Microcrystalline cellulose is purified, partially depolymerized cellulose that occurs as a white, odorless, tasteless, crystalline powder composed of porous particles. It is commercially available in different particle sizes and moisture grades that have different properties and applications.

Typical Properties:

Angle of repose: 49^0 for Ceolus KG; 34.4^0 for Emcocel 90M.

Density (bulk): 0.337 g/cm^3; 0.32 g/cm^3 for Avicel PH-101; 0.29 g/cm^3 for Emcocel 90M; 0.29 g/cm^3 for VivaPur 101.

Density (tapped): 0.478 g/cm^3; 0.45 g/cm^3 for Avicel PH-101; 0.35 g/cm^3 for Emcocel 90M.

Density (true): 1.512–1.668 g/cm^3

Flowability: 1.41 g/s for Emcocel 90M.

Melting point: chars at 260–270^0C.

Moisture content: typically less than 5% w/w. However, different grades may contain varying amounts of water. Microcrystalline cellulose is hygroscopic.

Applications:

Microcrystalline cellulose is widely used in pharmaceuticals, primarily as a binder/diluent in oral tablet and capsule formulations where it is used in both wet-granulation and direct-compression processes. In addition to its use as a binder/diluent, microcrystalline cellulose also has some lubricant and disintegrant properties that make it useful in tableting. Microcrystalline cellulose is also used in cosmetics and food products.

Magnesium stearate[36]

Non proprietary names:

BP: Magnesium stearate

JP: Magnesium stearate

PhEur: Magnesii stearas

USPNF: Magnesium stearate

synonyms:

Magnesium octadecanoate; octadecanoic acid, magnesium salt; stearic acid, magnesium salt.

Chemical Name and CAS Registry Number:

Octadecanoic acid magnesium salt [557-04-0]

Empirical Formula and Molecular Weight:

$C_{36}H_{70}MgO_4$ 591.34

The USPNF 23 describes magnesium stearate as a compound of magnesium with a mixture of solid organic acids that consists chiefly of variable proportions of magnesium stearate and magnesium palmitate ($C_{32}H_{62}MgO_4$). The PhEur 2005 describes magnesium stearate as a mixture of magnesium salts of different fatty acids consisting mainly of stearic acid and palmitic acid and in minor proportions other fatty acids.

Structural Formula:

$[CH_3(CH_2)_{16}COO]_2Mg$

Functional Category

Tablet and capsule lubricant.

Applications in Pharmaceutical Formulation or Technology:

Magnesium stearate is widely used in cosmetics, foods, and pharmaceutical formulations. It is primarily used as a lubricant in capsule and tablet manufacture at concentrations between 0.25% and 5.0% w/w. It is also used in barrier creams[43]

Talc:[37]

Synonyms:

Altalc; E553b; hydrous magnesium calcium silicate; hydrous magnesium silicate; Luzenac Pharma; magnesium hydrogen metasilicate; MagsilOsmanthus; Magsil Star; powdered talc; purified French chalk; Purtalc; soapstone; steatite; Superiore.

Chemical Name: Talc

Functional Category:

Anti-caking agent;glidant; diluent andlubricant.

Description:

Talc is a very fine, white to greyish-white, odourless, impalpable, unctuous, crystalline powder.

Typical Properties:

Specific gravity: 2.7–2.8

Specific surface area: 2.41–2.42 m^2/g

Solubility:

It is practically insoluble in dilute acids, alkalis, organic solvents and water.

Applications:

Talc is widely used in oral solid dosage formulations as a lubricant and diluents. It is widely used as a dissolution retardant in the development of controlled-release products. It is also used as an adsorbant. In topical preparations, talc is used as a dusting powder. Talc is additionally used to clarify liquids and is also used in cosmetics and food products.

Stability and Storage Conditions:

Talc is a stable material and may be sterilized by heating at 160^{o}C for not less than 1 hour. Talc should be stored in a well-closed container in a cool, dry place.

Incompatibilities: It is incompatible with quaternary ammonium compounds.

Safety:

Talc is regarded as an essentially nontoxic material. Inhalation of talc causes irritation and may cause severe respiratory distress in infants.

SODIUM BICARBONATE: [38]

Nonproprietary Names:

- BP : Sodium bicarbonate
- JP : Sodium bicarbonate
- PhEur : Natrii hydrogenocarbonas
- USP : Sodium bicarbonate

Synonyms:

Baking soda; E500; Effer-Soda; monosodium carbonate; Sal de Vichy; sodium acid carbonate; sodium hydrogen carbonate.

Chemical Name and CAS Registry Number:

Carbonic acid monosodium salt [144- 55-8]

Empirical Formula and Molecular Weight: NaHCO3 84.01

Functional Category: Alkalizing agent; therapeutic agent.

Applications: Sodium bicarbonate is generally used in pharmaceutical formulations as a source of carbon dioxide in effervescent tablets and granules. It is also widely used to produce or maintain an alkaline pH in a preparation.

Tablets may also be prepared with Sodium bicarbonate alone since the acid of gastric fluid is sufficient to cause effervescence and disintegration. Sodium bicarbonate is also used in tablet formulations to buffer drug molecules that are weak acids, thereby increasing the rate of tablet dissolution and reducing gastric irritation. The effects of tablet binders, such as polyethylene glycols, Microcrystalline cellulose, silicified Microcrystalline cellulose, pregelatinized starch, and povidone, on the physical and mechanical properties of Sodium bicarbonate tablets have also been investigated. Additionally, Sodium bicarbonate is used in solutions as a buffering agent for Erythromycin, Lidocaine, local anesthetic solutions, and total parenteral nutrition solutions. In some parenteral formulations, e.g., in Niacin parenteral formulation, Sodium bicarbonate is used to produce a sodium salt of the active ingredient that has enhanced solubility. Sodium bicarbonate has also been used as a freeze-drying stabilizer and in toothpastes. Recently, Sodium bicarbonate has been used as a gas-forming agent in alginate raft system and in floating, controlled-release oral dosage forms of Furosemide and Cisapride Tablet formulations containing Sodium bicarbonate have been shown to increase the absorption of Paracetamol, and improve the stability of Levothyroxine. Sodium bicarbonate is used in food products as an alkali or as a leavening agent, e.g. baking soda.

Table no 4: Uses of sodium bicarbonate

Use	Concentration (%)
Buffer in tablets	10-40
Effervescent tablets	25-50
Isotonic injection/infusion	1.39

Use Concentration (%) Buffer in tablets 10–40 Effervescent tablets 25–50 Isotonic injection/infusion 1.39

Description:

Sodium bicarbonate occurs as an odorless, white, crystalline powder with a saline, slightly alkaline taste. The crystal structure is monoclinic prisms. Grades with different particle sizes, from a fine powder to free-flowing uniform granules, are commercially available.

Typical Properties:

Acidity/alkalinity: pH = 8.3 for a freshly prepared 0.1 M aqueous solution at 25°C; alkalinity increases on standing, agitation, or heating.

Density (bulk): 0.869 g/cm3

Density (tapped): 1.369 g/cm3

Density (true): 2.173 g/cm3

Freezing point depression: 0.381°C (1% w/v solution)

Melting point: 270°C (with decomposition)

Moisture content: below 80% relative humidity, the moisture content is less than 1% w/w. Above 85% relative humidity, sodium bicarbonate rapidly absorbs excessive amounts of water and may start to decompose with loss of carbon dioxide.

Osmolarity: 1.39% w/v aqueous solution is isoosmotic with serum.

Refractive index: n20 D = 1.3344 (1% w/v aqueous solution)

Solubility:

Table no 5: Solubility of sodium bicarbonate.

Solvent Solubility	At 20^0C unless otherwise stated
Ethanol(95%)	Practically insoluble
Ether	Practically insoluble
Water	1 in 4 at 100^0C
	1 in 10 at 25^0C
	1 in 12 at 18^0C

Solvent Solubility at 20°C unless otherwise stated Ethanol (95%) Practically insoluble Ether Practically insoluble 1 in 11 1 in 4 at 100°Ca 1 in 10 at 25°C Water 1 in 12 at 18°C

Stability and Storage Conditions:

When heated to about 50°C, Sodium bicarbonate begins to dissociate into carbon dioxide, sodium carbonate, and water; on heating to 250–300°C, for a short time, Sodium bicarbonate is completely converted into anhydrous sodium carbonate. The effects of relative humidity and temperature on the moisture sorption and stability of Sodium bicarbonate powder have been investigated. Sodium bicarbonate powder is stable below 76% relative humidity at 25°C and below 48% relative humidity at 40°C.At 54% relative humidity, the degree of pyrolytic decarboxylation of Sodium bicarbonate should not exceed 4.5% in order to avoid detrimental effects on stability.At ambient temperatures, aqueous solutions slowly decompose with partial conversion into the carbonate; the decomposition is accelerated by agitation or heat. Aqueous solutions of Sodium bicarbonate may be sterilized by filtration or autoclaving. To minimize decomposition of Sodium bicarbonate by decarboxylation on autoclaving, carbon dioxide is passed through the solution in its final container, which is then hermetically sealed and autoclaved. The sealed container should not be opened for at least 2 hours after it has returned to ambient temperature, to allow time for the complete reformation of the bicarbonate from the carbonate produced during the heating process.Sodium bicarbonate is stable in dry air but slowly decomposes in moist air and should therefore be stored in a well-closed container in a cool, dry place.

Incompatibilities:

Sodium bicarbonate reacts with acids, acidic salts, and many alkaloidal salts, with the evolution of carbon dioxide. Sodium bicarbonate can also intensify the darkening of salicylates. In powder mixtures, atmospheric moisture or water of crystallization from another ingredient is sufficient for Sodium bicarbonate to react with compounds such as boric acid or alum. In liquid mixtures containing bismuth subnitrate, Sodium bicarbonate reacts with the acid formed by hydrolysis of the bismuth salt. In solution, Sodium bicarbonate has been reported to be incompatible with many drug substances such as Ciprofloxacin, Amiodarone, Nicardipine, and Levofloxacin.

Safety:

Sodium bicarbonate is used in a number of pharmaceutical formulations including injections and ophthalmic, otic, topical, and oral preparations. Sodium bicarbonate is metabolized to the sodium cation, which is eliminated from the body by renal excretion, and the bicarbonate anion, which becomes part of the body’s bicarbonate store. Any carbon dioxide formed is eliminated via the lungs. Administration of excessive amounts of Sodium bicarbonate may thus disturb the body’s electrolyte balance, leading to metabolic alkalosis. When used as an excipient, Sodium bicarbonate is generally regarded as an essentially nontoxic and nonirritant material. LD50 (mouse, oral) : 3.36 g/kg LD50 (rat, oral) : 4.22 g/kg Handling Precautions Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection and gloves are recommended.

Regulatory Status:

GRAS listed. Accepted for use as a food additive in Europe. Included in the FDA Inactive Ingredients Guide (injections; ophthalmic preparations; oral capsules, solutions, and tablets). Included in parenteral (intravenous infusions and injections) and nonparenteral medicines (ear drops, eye lotions, oral capsules, chewable tablets, effervescent powders, effervescent tablets, granules, tablets, suppositories and suspensions) licensed in the UK

CITRIC ACID : [39]

Nonproprietary Names

BP: Citric Acid Monohydrate

JP: Citric Acid Hydrate

PhEur: Citric Acid Monohydrate

USP: Citric Acid Monohydra

SYNONYMS:

Acidum citricum monohydricum; E330; 2-hydroxypropane-1,2,3-

tricarboxylic acid monohydrate.

CHEMICAL NAME:

2-Hydroxy-1,2,3-propanetricarboxylic acid

4 Empirical Formula and Molecular Weight

C6H8O7_H2O 210.14

FUNCTIONAL CATEGORY :

Acidifying agent; antioxidant; buffering agent; chelating agent;

flavor enhancer; preservative.

APPLICATIONS :

Citric acid (as either the monohydrate or anhydrous material) is widely used in pharmaceutical formulations and food products, primarily to adjust the pH of solutions. It has also been used experimentally to adjust the pH of tablet matrices in enteric-coated formulations for colon-specific drug delivery.(1) Citric acid monohydrate is used in the preparation of effervescent granules, while anhydrous citric acid is widely used in the preparation of effervescent tablets.(2–4) Citric acid has also been shown to improve the stability of spray-dried insulin powder in inhalation formulations. In food products, citric acid is used as a flavor enhancer for itstart, acidic taste. Citric acid monohydrate is used as a sequestering agent and antioxidant synergist; see Table I. It is also a componentof anticoagulant citrate solutions. Therapeutically, preparations containing citric acid have been used to dissolve renal cal.

HYDROXY PROPYL METHYL CELLOLOSE:[39]

Synonyms	**:**	Benecel, HPMC, Methocel. ,Hypromellose
Chemical Name	**:**	Cellulose Hydroxy propyly methyl ether
Empirical formula	**:**	CH_3 CH_2 (OH) CH_3
Description	**:**	white or creamy white fibrous or granular, odorless, tasteless.

Melting point	**:**	Browns at 190-200 ^{o}C Chars at 225-230 ^{o}C
Stability	**:**	Stable between pH 3-11.
Applications	**:**	To retard the release of drugs from a matrix in tablets and capsules. Also used as binder and in tablet coating.
Functional Category	**:**	Bioadhesive material; coating agent; controlled-release agent; dispersing agent; dissolution enhancer; emulsifying agent; emulsion stabilizer; extended-release agent; film-forming agent; foaming agent; granulation aid; modified release agent; mucoadhesive; release-modifying agent; solubilizing agent; stabilizing agent; suspending agent; sustained-release agent; tablet binder; thickening agent; viscosity-increasing agent.
Applications	**:**	Hypromellose is widely used in oral, ophthalmic, nasal, and topical pharmaceutical formulations. In oral products, hypromellose is primarily used as a tablet binder, in film coating, and as a matrix for use in extended release tablet formulations. High-viscosity grades may be used to retard the release of drugs from a matrix in tablets and capsules. Hypromellose is also used in liquid oral dosage forms as a suspending and/or thickening agent.

LITERATURE REVIEW

1Nalle Suhas *et al.*,(2009)[15] prepared design and evaluation of controlled release Nateglinide tablets using Hydrophilic polymer formulated by using polymers such as HPMC, MC and Na CMC as release retardants. It was observed that the type of polymer and its concentration has influenced the drug release from matrix tablets.

2 Mukesh C. Gohel *et al.*,(2009)[16] concluded that it was possible to fabricate modified release tablets of Metoprolol Succinate ER tablets Using HPMC K100M and Xanthan gum. The combination of matrixing agents namely xanthan gum and HPMC K100M overcomes disadvantages of each polymer. The initial drug burst release was controlled by quick gelation of Xanthan gum where as subsequent drug release and matrix integrity were maintained by firm gel of HPMC K 100M. The drug release was found to be dependent on the amount and type of matrixing agent.

3 N.N.Rajendran *et al.*, (2009)[17]conclusively stated that development of extended release formulation of hydrophilic drugs does not necessitate the inclusion of hydrophobic polymers to hydrophilic polymers and the desired extended release of hydrophilic drugs is also viable with hydrophilic polymer alone.

4 Antesh K Jha *et al.*, (2009)[18]concluded that the hydrophilic matrix of HPMC alone could not control the Metoprolol Succinate release effectively for 16 hours and the matrix tablets prepared with HPMC and a granulating agent of a hydrophobic polymer was a better system for once daily sustained release of a highly water soluble drugs like Metoprolol Succinate.

5 R Enayatifard *et al.*, (2009**)**[19]demonstrated that HPMC and EC could slow down the release profile of diltiazem HCl from their matrices. Incorporation of EC in HPMC matrix tablets was found to control drug release.

6 Zafar Iqbal *et al.*, (2010)[20]prepared and evaluated matrix tablets of Diclofenac Sodium using PVP K90 and natural polymers and concluded that PVP K90 and gum at the drug: polymer ratio 1:3 sustained the release of the drug for about 12 hours. The addition of the buffers increase the initial release of the diclofenac from the dosage form however, drug release was sustained for about 10 hours. The combination of PVP K90 and natural gum also sustained the release of the diclofenac sodium for about 12 h however, the best similarity and differential factors were obtained with the combination of PVP K90 and gum tragacanth.

7 Madhusudhan pogula *et al.*, (2010)[21]concluded that the use of microcrystalline cellulose one can achieve the tablets with good hardness and also concluded that HPMC K 100 shows better drug control compared to HPMC E 4 M.

8 Prajapati B. G. *et al*.,(2010)[22] prepared once daily sustained release matrix tablets of Losartan Potassium and concluded that HPMC alone could not control the Losartan Potassium release effectively for 24 hrs. It was evident from the results that a matrix tablet prepared with hydrophilic polymer and hydrophobic polymer was a better system for once daily sustained release of a highly water soluble drug like Losartan Potassium.

9 Marina Koland *et al.*,(2010)[23] prepared mucoadhesive films of Losartan Potassium for buccal delivery using HPMC and retardent polymers Ethyl cellulose or Eudragit RS 100 and concluded that it was possible to formulate mucoadhesive films of Losartan Potassium with the intention of obtaining better therapeutic efficiency by controlling drug release thereby improving patient compliance and increasing bioavailability with decreased dosing and fewer side effects. The use of retardent polymers succeeded in delaying drug release, however, higher percentage of these tend to decrease the mucoadhesive properties.

10 Jaimini Manish *et al*.,(2011) [24] Formulated and evaluated floating effervescent matrix tablets of Losartan potassium by using two different grades of methocel K100 and K15 by effervescent technique. The effect of citric acid and two different grades of methocel on drug release profile and floating property were investigated. A combination of sodium bi carbonate and citric acid was found to achieve optimum in vitro buoyancy. It was observed that tablet remain float for 8-10 hrs. The tablets with high grades of methocel (K100) were found to float for longer duration as compared with formulations containing methocel K15M.

11 Naveen M *et al.*, (2011)[25] Formulated and evaluated floating tablets of Losartan potassium by direct compression method using sodium bicarbonate as the effervescent base. HPMC K4M, HPMCK15M, HPMC K100M, were used as polymers to prepare the floating tablets and to study the drug release for 12hr in stomach. It was found that the dimensional stability of the formulations increase with increasing concentration of the swelling agent.

12 A.Suman *et al.*,(2011)[26] Formulated and evaluated Losartan potassium floating tablets by using HPMC K100M, HPMC K15M, HPMC K4M, by effervescent technique. Sodium bicarbonate was incorporated as a gas-generating agent. The floating tablets were evaluated for physical characteristics, the tablet swelled radially and axially during in vitro buoyancy studies.

HPMC K100 based matrix tablets showed significantly greater swelling indices compared with other batches. The tablets exhibited prolonged drug release profiles while floating over the dissolution medium.

13 Lingaraj S. Danki *et al.*,(2011)[27] Developed and evaluated gastro retentive drug delivery system of Losartan Potassium. Formulations were prepared using wet granulation method, employing polymers like HPMCK4M, HPMC K15M, carbopol 934P and sodium alginate. Sodium bicarbonate and citric acid were used as gas generating agents. Tablets were evaluated for polymer interaction studies, swelling index, in vitro floating studies, In vitro drug release and short term stability studies. Drug release analysis on the basis of Higuchi-Korsmeyer model indicated that diffusion is the predominant mechanism controlling the drug release.

14 Parikh Bhavik Anjankumar *et al.*,(2011)[28] Formulation and Evaluation of Floating Tablet of Atenolol: Functionality of Natural and Synthetic Polymer. The tablets were prepared by direct compression. The pre and post compression studies were performed. The release behavior of the natural and synthetic polymer was compared. According to obtained data, .natural polymer shows better sustained release properties than synthetic polymer. The formulation with guar gum and xanthum gum shows better sustained release effect than HPMC different grade.

15 R .Vijaya Muthumanikandar *et al.*,(2011)[29] Developed and evaluated buccoadhesive tablets of Losartan Potassium and concluded that Hardness of the Bioadhesive tablets varied with various type and ratio of the Bioadhesive polymers. The difference in the tablets hardness did not affect the release of the drug from the hydrophilic matrices which is release by diffusion through the gel layer and erosion of this layer and is therefore independent of the dry state of the tablet.

16 Mohd Azharuddin *et al.*, (2011)[30]Formulated and evaluated controlled release matrix tablets of antihypertensive drug Losartan Potassium using natural and synthetic hydrophilic polymers and concluded that the polymer concentration plays a major role in drug release. As the polymer concentration of the tablets increased the drug release was prolonged in a controlled manner.

17 Raju G *et al.*, (2012)[31]formulated and evaluated extended release tablets of Venlafaxine HCl better drug release control over an extended period time and also concluded that higher viscosity grades of polymer concentrations will retard the drug release effectively.

18 P Subhash Chandra Bose *et al.*, (2011)[32]formulated and evaluated sustained release tablets of Diltiazem HCl using xanthan gum and concluded that xanthan gum, a biodegradable polymer can be employed for use as a carrier in developing floating drug delivery systems.

19 Ganesan V *et al.,* (2008)[33]formulated and evaluated matrix tablets of Ambroxol HCl using guargum and concluded that slow, controlled and complete release of Ambroxol over a period of 12h was obtained from matrix tablets containing 30% w/w of low-viscosity, 25% w/w medium viscosity or 20% w/w high viscosity guar gum respectively.

20 Himansu bhusan samal *et al.,* (2011)[34]formulated and evaluated Zidovudine matrix tablets and concluded that stable formulation could be developed by incorporating both hydrophilic and hydrophobic polymers in a definite proportion so that sustained release profile is maintained for an extended periods of time.

METHODOLOGY

Materials used

Table no 6 : List of materials used

Sl. no	**Materials**	**Source**
1	Losartan Potassium	Gift sample from Hetero drugs pvt limited, hyderabad
2	HPMC E15	Lara drugs pvt limited, hyderabad
3	HPMC K15	Lara drugs pvt limited, hyderabad
4	Microcrystalline cellulose	Yarrow chem products, Mumbai
5	Sodium bi Carbonate	Lara drugs pvt limited, hyderabad
6	Citric Acid	Lara drugs pvt limited, hyderabad
7	Talc	Molychem, Mumbai.
8	Magnesium Sterate	Lara drugs pvt limited, hyderabad

Table no 7 : List of instruments used

Sl. no.	Instruments used	vendor
1	Digital balance	Sartorius
2	Hot air oven	Lab india
3	Monsanto Hardness tester	Lab india.
4	Friabilator, model:EF-2	Lab india
5	pH meter, model:7007	Lab india
6	Rotary tablet punching machine	Elite scientific and equipment, Guntur.
7	Dissolusion apparatus(USP)Type-II	Lab india
8	UV-Visible spectrophotometer, model: SL-164 double beam.	Lab india
9	sonicator	Pci analytics
10	Vernier callipers	Mitutoyo corporation
11	Bulk density apparatus	Lab india
12	FT-IR spectrophotomer	Jasco

PRE FORMULATION STUDIES:

DRUG- EXCIPIENTS IN- COMPATIBILITY STUDIES:

Drug was mixed with excipients .about 5gms of blend was prepared , which were kept in 10 ml white colored glass vials and packed properly .these vials are exposed to room temperature and $40^0c\pm2^0C/75\pm5\%$ RH. Observations for physical appearance were made at zero weeks to 1 month, then the samples were withdrawn for analysis of appearance.The drug excipients interaction was investigated by FT-IR

FT-IR- SPECTROSCOPY:

Drug and excipients compatibility study is done by Fourier Transform Infrared Spectroscopy [FTIR]. FT-IR Spectra were obtained by using an FT-IR Spectroscopy-(PERKINELMER). The samples (pure drug) was previously ground and mixed throughly with KBr, an infrared transparent matrix at(sample/KBr) ratio respectively. the KBr discs were prepared by the compressing the powders at a pressure of 5 tons for 5min in a hydraulic press (40 scans were obtained at a resolution $4cm^{-1}$ from $4600\text{-}300cm^{-1}$).

The compatibility studies provide the frame work for the drugs combination with the excipients in the fabrication of the dosage form. The study was carried out to establish that the therapeutically active drug has not undergone any changes ,after it has been subjected to processing steps during formulation of tablets.

STANDARD CURVE OF LOSARTAN POTASSIUM[40]

Preparation of 0.1 N HCL:

8.5 ml of concentrated hydrochloric acid was diluted with distilled water and the volume was made upto 1000 ml with distilled water.

Preparation of Losartan potassium standard stock solution in o.1N HCL:

A Standard solution of Losartan Potassium was prepared by dissolving accurately weighed 100 mg of Losartan potassium with little quantity of 0.1N HCL solution ,in a 100 ml volumetric flask.The volume was made up to 100 ml with 0.1N HCL to obtain a stock solution of 1000 mcg/ml .from the above solution several dilutions are made to obtain 50, 75,100, 125, 150 mcg/ml solutoions. The absorbance of these drug solutions were estimated at .λ_{max} 234 nm.

FORMULATION DEVELOPMENT AND EVALUATION

The active ingredient i.e. Losartan Potassium and each single polymer (HPMC E15) (HPMCK15) and also mixture of two polymers, filler (MCC), lubricant (Magnesium stearate) glidant (Talc) Floting (sodium bi carbonate and citric acid)were blended together by dry mixing in a laboratory mixer (polybag) for 10 mins. The mixture was compressed by using 8mm standard flat round punch and die set at compression force 4-6 ton.

8.1 Preparation of tablets by direct compression:

Direct compression

The ideal process from a capital and operational cost basis is direct compression. This is, at most, a two-step process involving screening and/or milling and final mixing. An effective excipient binder is needed and should have good compression and consolidation properties as a dry additive, even at low concentrations (< 30%) in the formulation. Good adhesive properties in the dry form are a combination of a rough and porous surface combined with a Vander Waal's and/or a hydrophilic bonding mechanism to attach the active ingredient(s) to the excipients. This feature is needed to assure good mixing of drug and excipients and to prevent segregation.

Advantages of direct compression

1. Economy in labor, time, equipment, operational energy, and space.
2. Problems due to heat and moisture eliminated.
3. Greater physical stability provided; hardness and porosity changes less with time when direct compression is broadly compared to wet granulation systems.
4. Extraction of the drug from the dosage form is not inhibited during the assay procedure (polymer binding).

Disadvantages of direct compression

1. Difficulty obtaining dense hard tablets for high-dose drugs.
2. No homogenous distribution of low-dose drugs due to segregation after blending (content uniformity).
3. Need for assisted feed and pre compressions for some high-dose drugs.
4. Need for commensurate particle size or particle size distribution between drug and excipients.

Table no 8: Formulation of Losartan potassium

	Quantity per batch (mg/tab)					
INGREDIENTS	**F-1**	**F-2**	**F-3**	**F-4**	**F-5**	**F-6**
Losartan Potassium	50	50	50	50	50	50
HPMC(E15)	--	--	200	--	200	200
HPMC K(15)	50	200	--	--	--	--
HPMC(E15)+HPMCK(15)	--	--	--	100+100	--	--
Microcrystalline cellulose	201	51	51	51	65	75
Sodium bi carbonate	30	30	30	30	20	10
Citric acid	5	5	5	5	5	5
Talc	7	7	7	7	5	5
Magnesium Sterate	7	7	7	7	5	5
Total weight	350	350	350	350	350	350

PRE-COMPRESSION EVALUATION PARAMETERS

Angle of repose:

The angle of repose of powder blend was determined by the funnel method. The accurately weigh powder blend were taken in the funnel. The height of the funnel was adjusted in such a way the tip of the funnel just touched the apex of the powder blend. The powder blend was allowed to flow through the funnel freely on to the surface. The diameter of the powder cone was measured and angle of repose was calculated using the following equation.

$$\tan\theta = \frac{h}{r}$$

Where,

h and r are the height and radius of the powder cone.

Table no 9: Comparison between angle of repose and flow properties[41]

Angle of repose (θ)	Flow
< 25	Excellent
25 – 30	Good
30 – 40	Moderate (addition of 0.2% glidant required)
> 40	Poor

Bulk density:

Both bulk density (BD) and tapped density (TD) was determined. A quantity of 10 gm of powder blend from each formula, previously shaken to break any agglomerates formed, was introduced in to 50 ml measuring cylinder. After that the initial volume was noted and the cylinder was allowed to fall under its own weight on to a hard surface from the height of 2.5 cm at second intervals. Tapping was continued until no further change in volume was noted. Bulk density(BD) and Tapped density (TD) were calculated using the following equations.

$$\mathrm{BD} = \frac{\text{Weight of the powder blend}}{\text{Untapped Volume of the packing}}$$

$$\mathrm{TD} = \frac{\text{Weight of the powder blend}}{\text{Tapped Volume of the packing}}$$

Table no 10: Flowability according to Hausner’s ratio

Hausner’s ratio	Flow character
1.0-1.11	Excellent
1.12-1.18	Good
1.19-1.25	Fair
1.26-1.34	Passable
1.35-1.45	Poor
1.46-1.59	Very poor
> 1.60	Very, very poor

Compressibility index (Carr's Index):

Compressibility index is an important measure that can be obtained from the bulk and tapped densities. In theory, the less compressible a material the more flowable it is. A material having values of less than 20% has good flow property.[42,43,44]

.

$$C_I = \frac{(\text{Tapped density} - \text{Bulk density})}{\text{Tapped Density}} \times 100$$

Table no 11:Properties of compressibility index

% Comp. Index	Properties
5-12	Free flowing
12-16	Good
18-21	Fair
23-35	Poor
33-38	Very poor
>40	Extremely poor

POST COMPRESSION EVALUATION PARAMETERS[45]

The tablets were evaluated for in process and finished product quality control tests i.e. appearance, dimensions (diameter and thickness), weight variation, hardness, friability, assay, and drug content.

Physical appearance:

The general appearance of tablets, its visual identity and overall elegance is essential for consumer acceptance. the control of general appearance of tablet involves measurement of number of attributes such as tablet size, shape, colour presence or absence of odour, taste, surface texture and constituency of any identification of marks.

Thickness:

10 tablets were measured for their and diameter with a vernier caliper. thickness Guage average thickness and diameter were calculated.

Weight variation:

The weight of the tablet being made was routinely determined to ensure that a tablet contains the proper amount of drug. The USP weight variation test is done by weighing 20 tablets individually, calculating the average weight and comparing the individual weights to the average. The tablets met the USP specification that not more than 2 tablets are outside the percentage limits and no tablet differs by more than 2 times the percentage limit. USP official limits of percentage deviation of tablet are presented in the table.

Table no 12: Weight variation limits

S. No.	Average weight of tablet (mg)	Maximum % difference allowed
1	130 or less	10
2	130-324	7.5
3	>324	5

Tablet hardness:

The resistance of tablets to shipping or breakage under conditions of storage, transportation and handling before usage depends on its hardness. The hardness of each batch of tablet was checked by using Monsanto hardness tester. The hardness was measured in terms of kg/cm^2. 3 tablets were chosen randomly and tested for hardness. The average hardness of 3 determinations was recorded.

Friability:

Friability generally refers to loss in weight of tablets in the containers due to removal of fines from the tablet surface. Friability generally reflects poor cohesion of tablet ingredients.

Method

10 tablets were weighed and the initial weight of these tablets was recorded and placed in Roche friabilator and rotated at the speed of 25 rpm for 100 revolutions. Then tablets were removed from the friabilator, dusted off the fines and again weighed and the weight was recorded.

$$\text{friability} = \frac{(w_1 - w_2)}{w_1} \times 100$$

Where, w_1= weight of the tablet before test. .

w_2 = weight of the tablet after test.

***IN-VITRO* BUOYANCY STUDIES:**

The in vitro buoyancy was determined by floating lag time .The tablets were placed in a 100 ml beaker containing 0.1N hydrochloric acid. The time required for the tablet to rise to the surface and to float was determined as **floating lag time.** The duration of time for which the dosage form constantly remained on the surface of medium was determined as the **total floating time**.

Drug content:

twenty tablets were taken, powdered and the powder equivalent to one dose each was transferred to a 100 ml volumetric flask and 0.1N HCL. The solution was filtered and diluted suitably and drug content in the sample was estimated using UV-Visible spectrophotometer at 234 nm.

IN-VITRO DISSOLUTION STUDIES:[46]

The *In-vitro drug* release study was performed for all the tablets using USP type II dissolution apparatus under the following conditions.

Dissolution test parameters:

Medium	:	900 ml of 0.1 N HCL
Temperature	:	$37^0 \pm 0.5^0$c
RPM	:	50
Sampling volume	:	5 ml
Sampling time	:	1, 4, 8, 16, 20 hours

Preparation of 0.1 N HCL:

Take 8.5 ml of concentrated hydrochloric acid in a 1000 ml volumetric flask and make up the volume.

Procedure:

Tablet was introduced into dissolution test apparatus and the apparatus was set as 50 rpm .5 ml of sample was withdrawn at the predetermined time intervals. samples were analyzed by UV spectrophotometer at 234 nm using 0.1 N HCL solution as blank.

STABILITY STUDIES:[47]

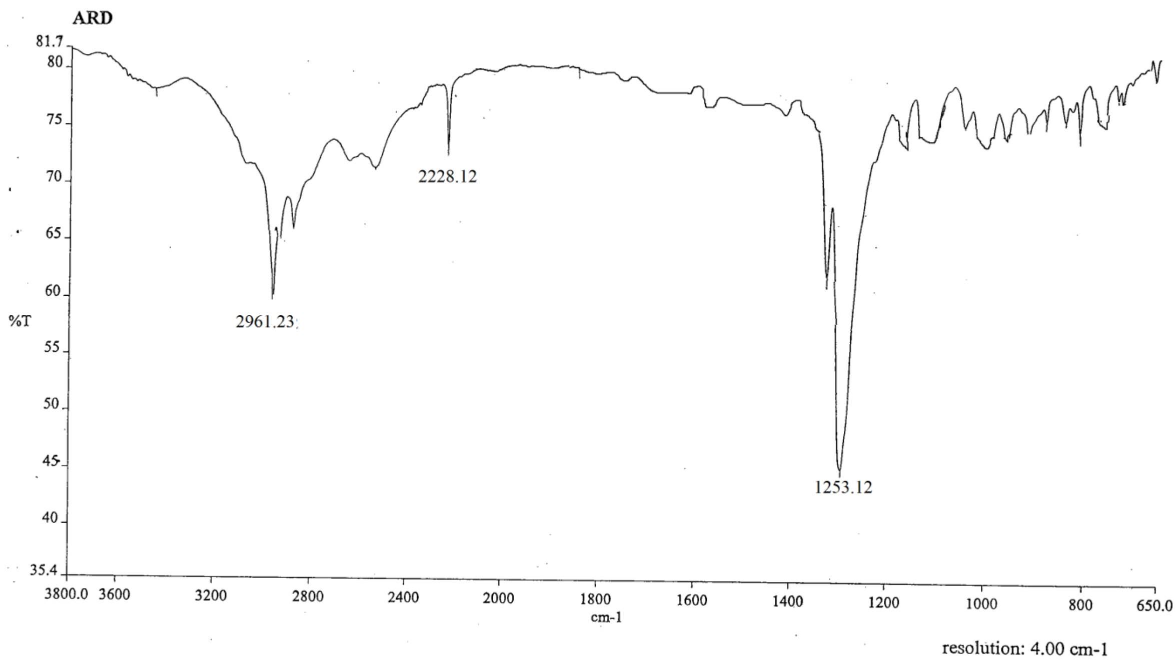
The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety environmental factors , such as temperature , humidity etc .the product is subjected to short time studies at 40^{0}C ± 2^{0}C / 75**%**±5%RH for 3months.

RESULTS AND DISCUSSION

Table no13: DRUG-EXCIPIENTS PHYSICAL IN COMPATABILITY STUDIES:

S.NO	INGREDIENTS	RATIO	DESCRIPTION	
			INTIAL	AFTER 1 MONTH AT (40^0C;75%RH)
1	LOSARTAN POTASSIUM -API	1	WHITE TO OFF WHITE POWDER	NCC
2	API±HPMC E15	1:1	WHITE TO OFF WHITE POWDER	NCC
3	API±HPMC K15	1:1	WHITE TO OFF WHITE POWDER	NCC
4	API±MCC	1:1	OFF WHITE POWDER	NCC
5	API±SODIUM BI CARBONATE	1:1	WHITE POWDER	NCC
6	API±CITRIC ACID	1:1	OFF WHITE POWDER	NCC
7	API±MAGNESIUM STEARATE	1:1	OFF WHITE POWDER	NCC
8	API±TALC	1:1	WHITE TO OFF WHITE POWDER	NCC

Fig no 2: FT-IR spectrum of pure drug



Figno3: Pure drug and HPMCE15

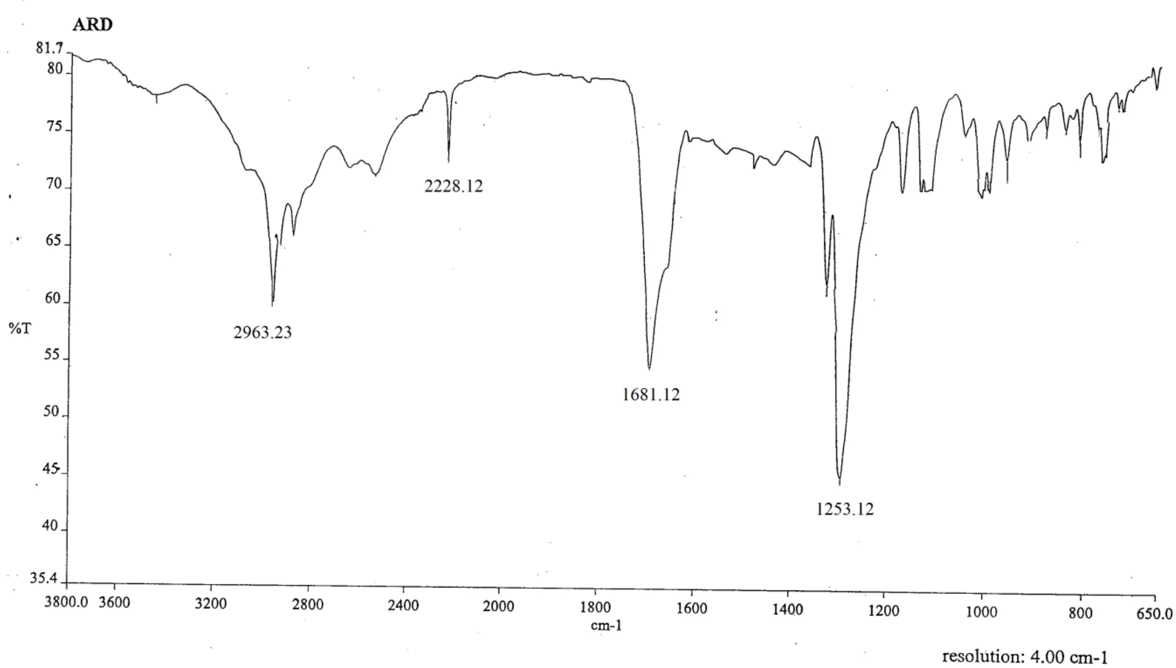


Fig no4: Pure drug and HPMC K15

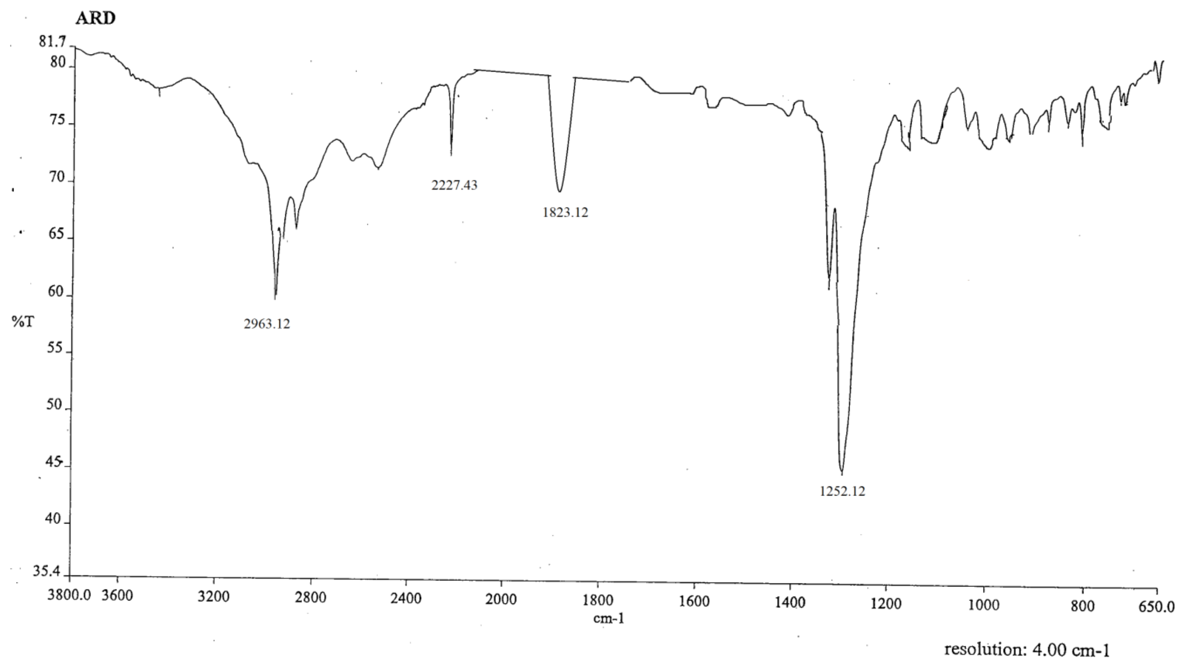


Fig no 5: Pure drug and MCC

Fig no 6: Pure drug with other excipients

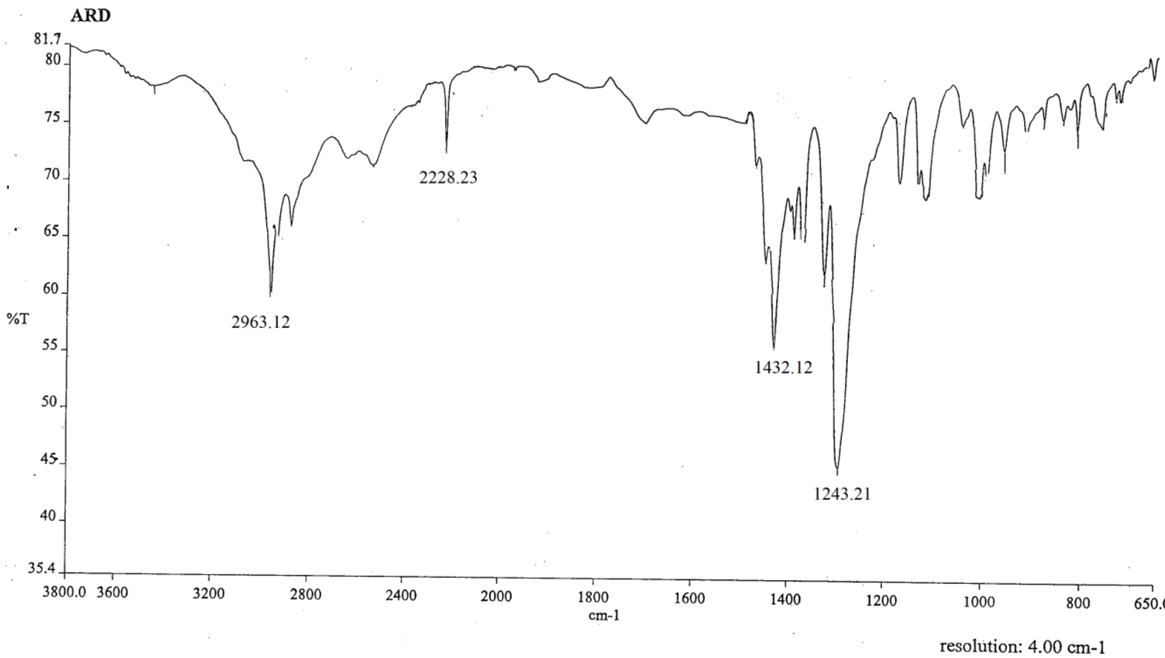


Table no:14 Absorbances for Calibration curve of Losartan Potassiuum

Sl. no	Concentration (mcg/mL)	Absorbance
1	0	0
2	5O	0.1929
3	75	0.2744
4	100	0.3462
5	125	0.4256
6	150	0.5110

Fig no 7: Calibration curve of Losartan Potassiuum

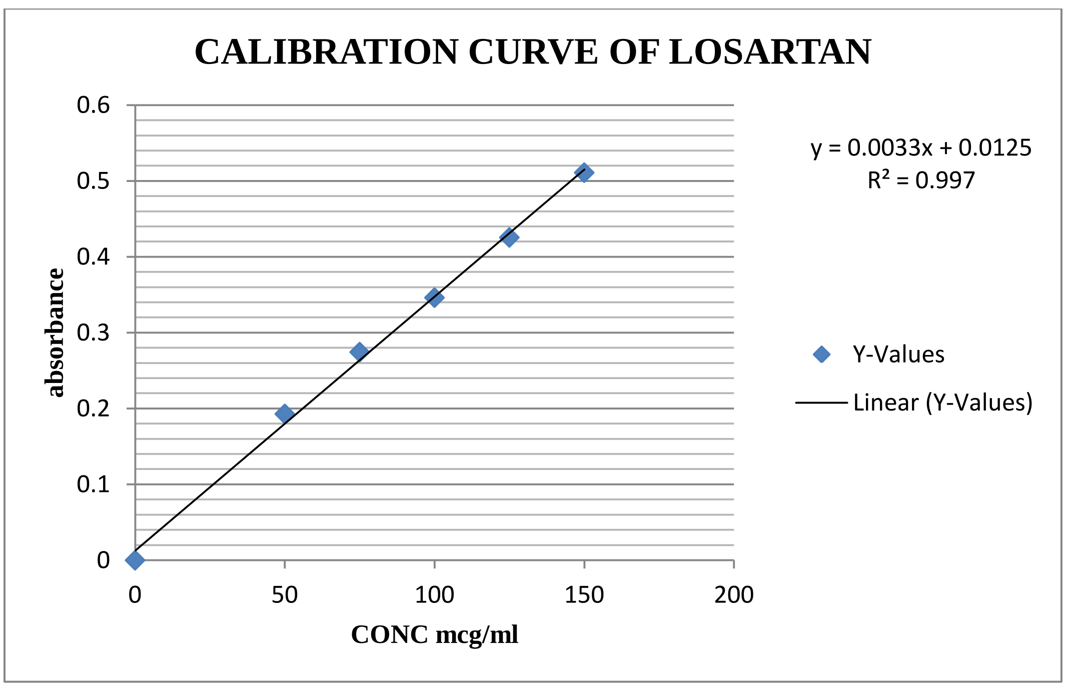


Table NO: 15 Data for Angle of repose

Formulation code	Angle of repose
F-1	$25.26^0 \pm 0.672$
F-2	$26.29^0 \pm 0.587$
F-3	$26.45^0 \pm 0.652$
F-4	$27.04^0 \pm 0.498$
F-5	$25.14^0 \pm 0.622$
F-6	26.38 ±0.595

Fig no 8: COMPARISON OF ANGLE OF REPOSE

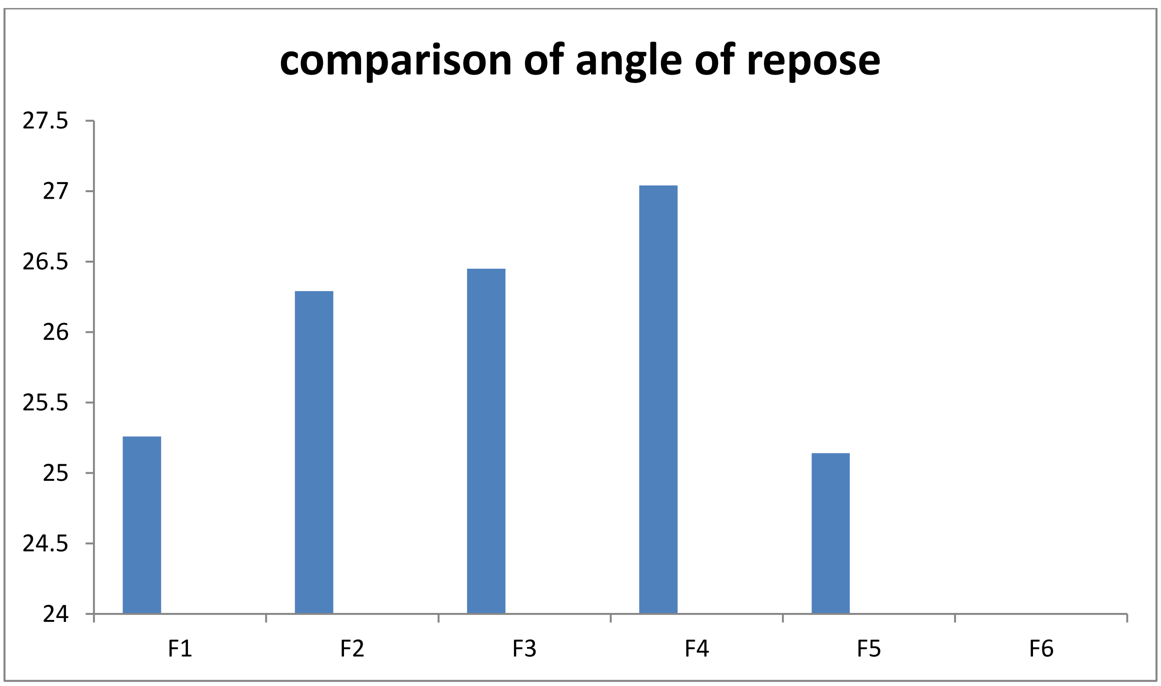


Table no16:Data for bulk density and tapped density

Formulation code	Bulk Density (gm/ml)	Tapped Density (gm/ml)
F-1	0.5384±0.191	0.5833±0.272
F-2	0.5599±0.0.281	0.6087±0.293
F-3	0.6087±0.281	0.6363±0.321
F-4	0.5384±0.191	0.6363±0.321
F-5	0.5599±0.221	0.6087±0.293
F-6	0.6087±0.281	0.6666±0.354

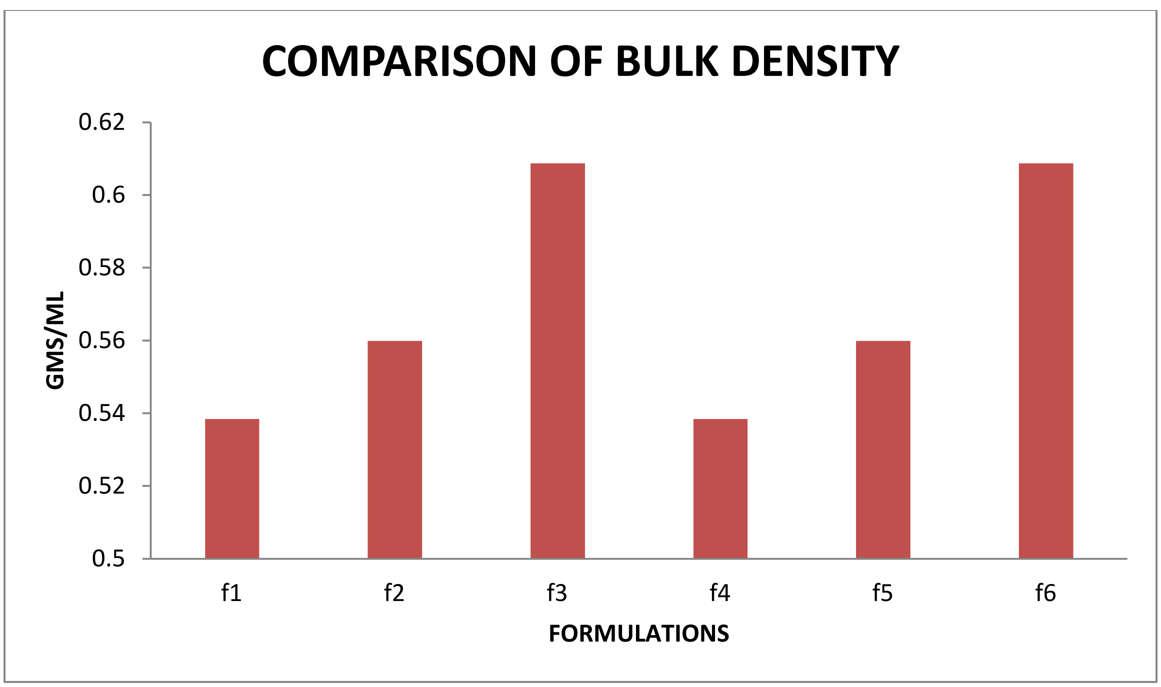
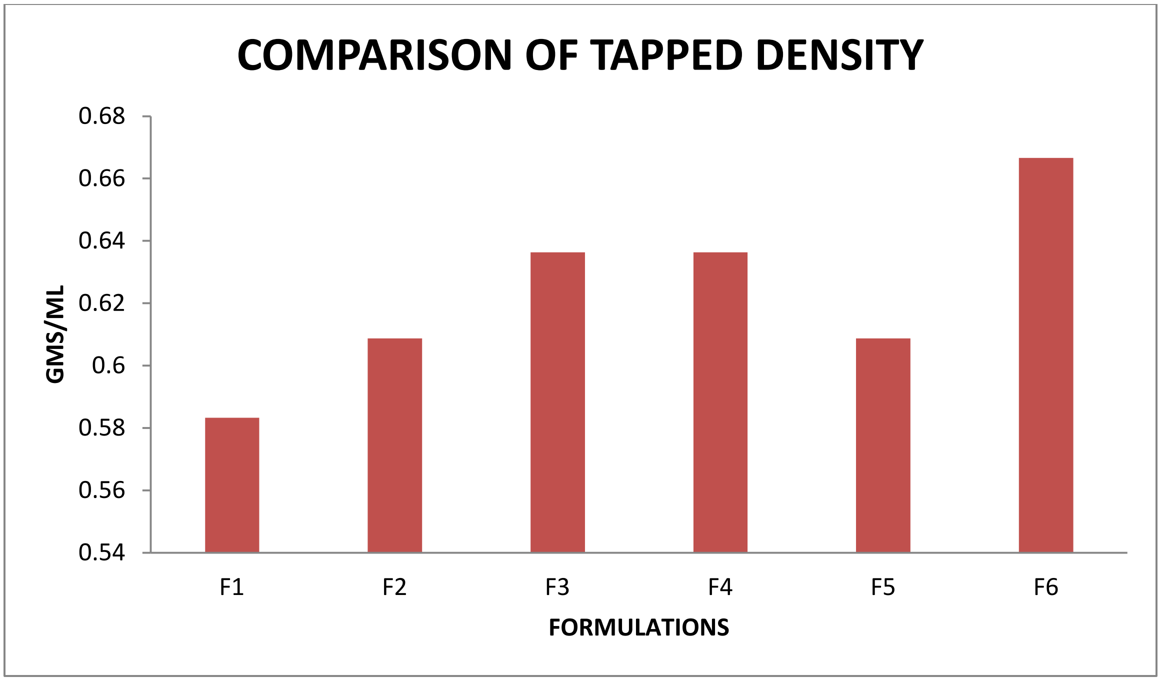


Fig no9: Comparison of bulk density



figno10: comparison of tapped density

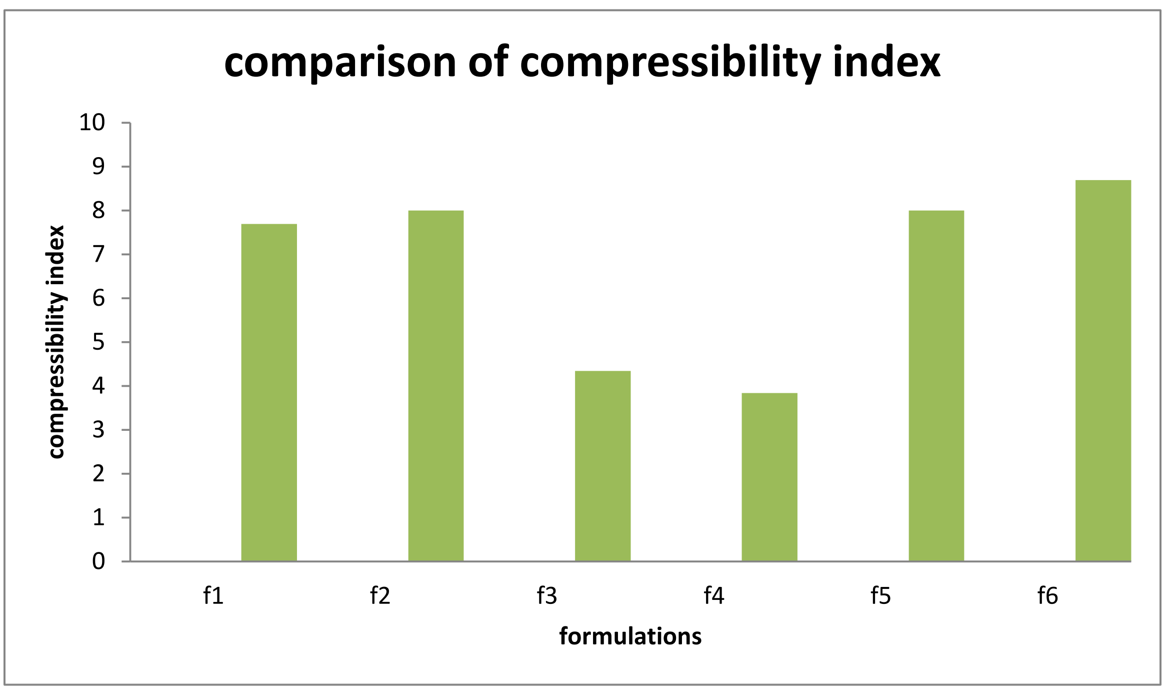


fig no:11 comparison of compressibility index

Fig no 12:comparison of Hauner's ratio

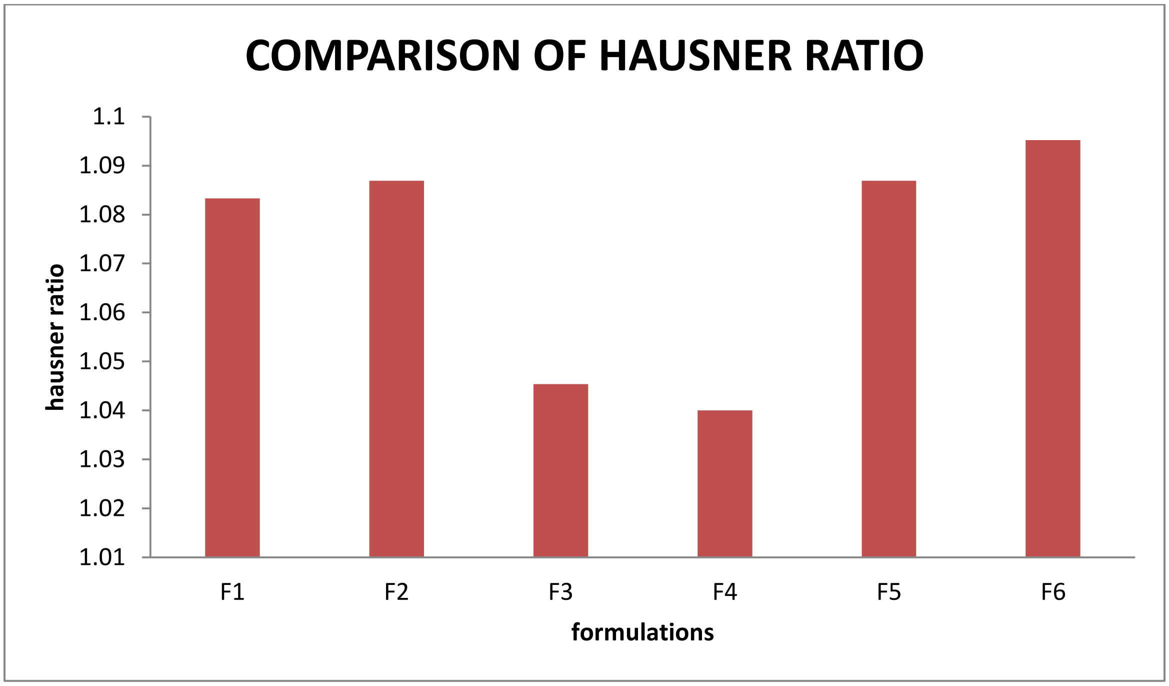


Table no17: Data for Hausner's ratio and Compressibility index:

Formulation code	Hausner's Ratio	Compressibility Index (%)
F-1	1.0833	7.6923
F-2	1.0869	8.000
F-3	1.0454	4.3478
F-4	1.0400	3.8461
F-5	1.0869	8.000
F-6	1.0952	8.6956

Evaluation of tests:

Table no 18: Data for Weight variation

Formulation code	Weight variation
F-1	352.4±4.3
F-2	351.1±2.9
F-3	350.5±2.4
F-4	348.4±2.1
F-5	353.9±5.9
F-6	355.4±6.2

Fig no 13: comparison of weight variation

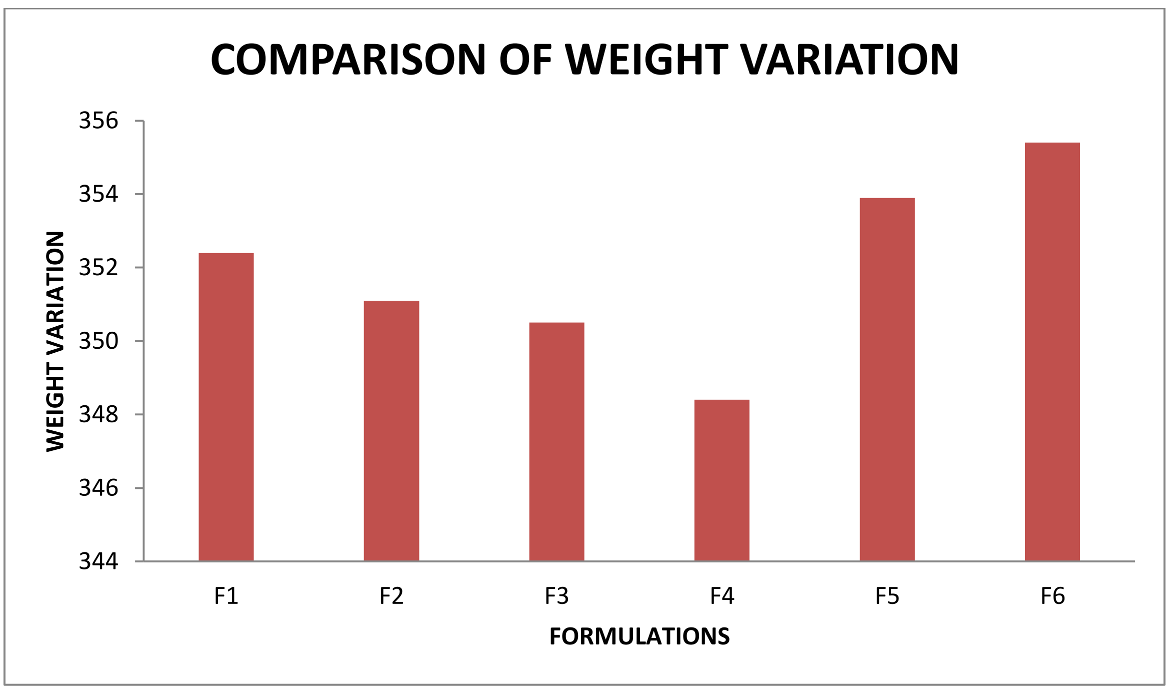


Table no 19 : Data for Hardness

Formulation code	Hardness test (Kg/cm^2) Avg ± SD (n=5)
F-1	4.3 ± 0.24
F-2	4.2 ± 0.24
F-3	4.7 ± 0.24
F-4	5.5 ± 0.24
F-5	4.3 ± 0.24
F-6	4.9 ± 0.20

Fig no14: Comparison of hardness

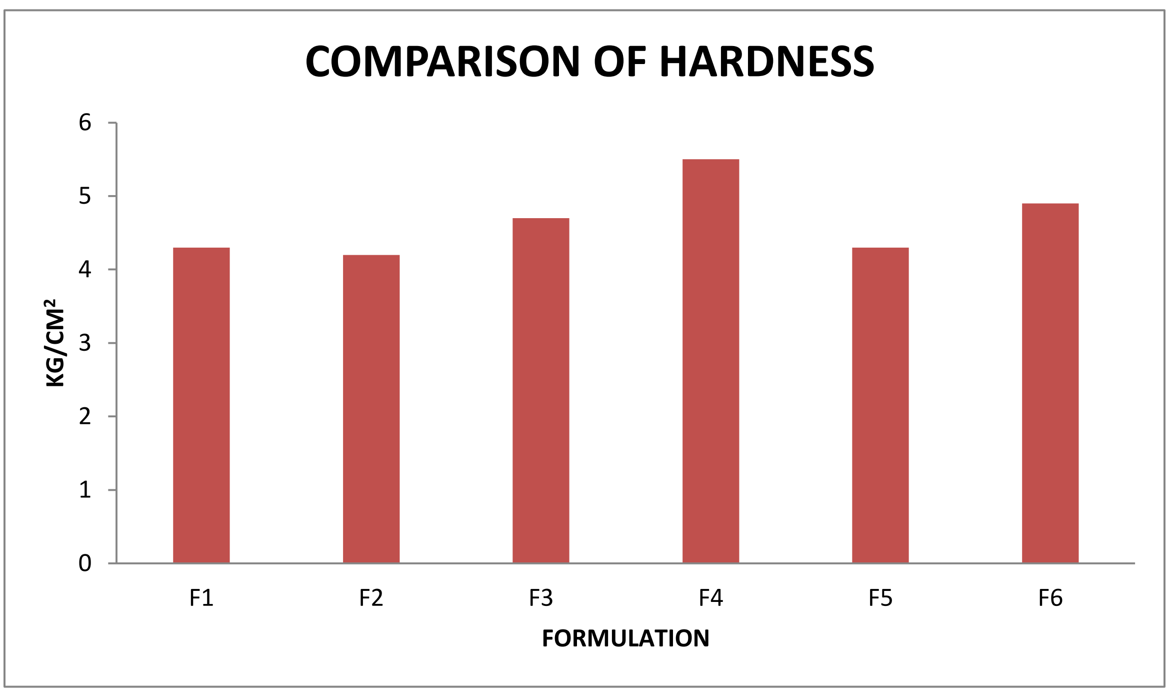


Table no 20 : Data for Friability

Formulation code	Friability (%)
F-1	0.28
F-2	0.37
F-3	0.25
F-4	0.18
F-5	0.48
F-6	0.74

Fig no15:Comparison of friability

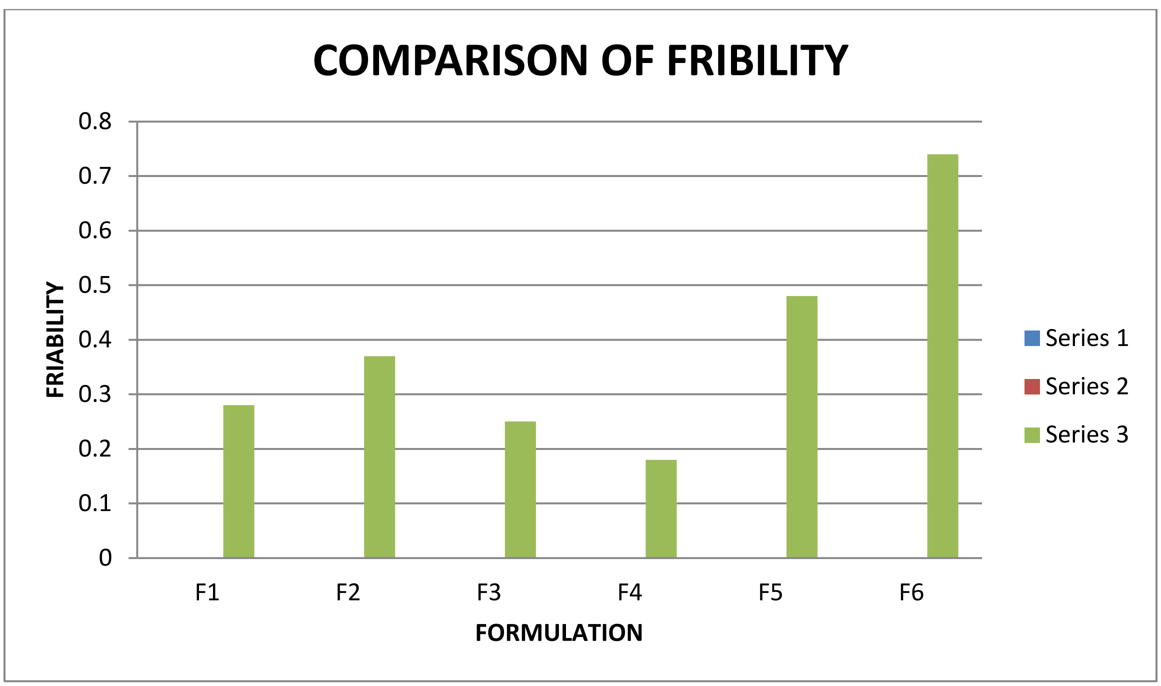


Table21 : Data for Thickness

Formulation code	Thickness(mm)
F-1	3.52±0.03
F-2	3.51± 0.01
F-3	3.53± 0.04
F-4	3.50± 0.01
F-5	3.52±0.03
F-6	3.53±0.04

Fig no16: comparison of thickness

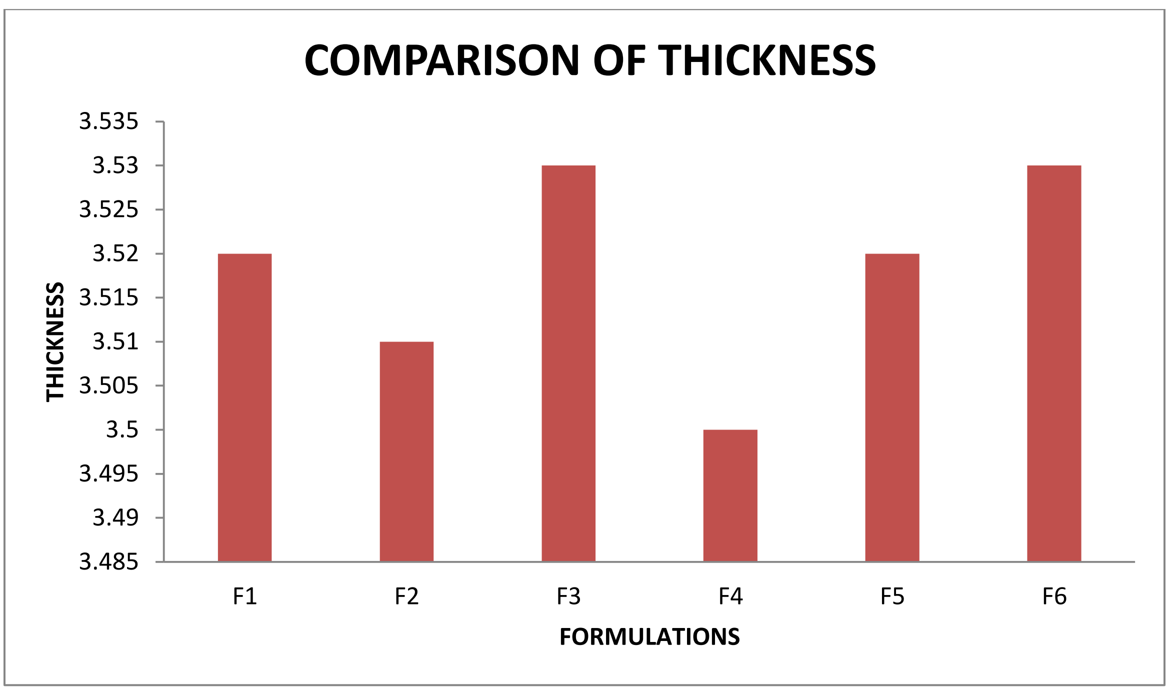


Table no 22: Data for floating lag time and total floating time

Formulation code	Floating lag time(sec)	Total floating time(hrs)
F-1	92	12
F-2	105	16
F-3	105	16
F-4	90	16
F-5	172	17
F-6	114	16

Fig no17:comparison of floating lag time

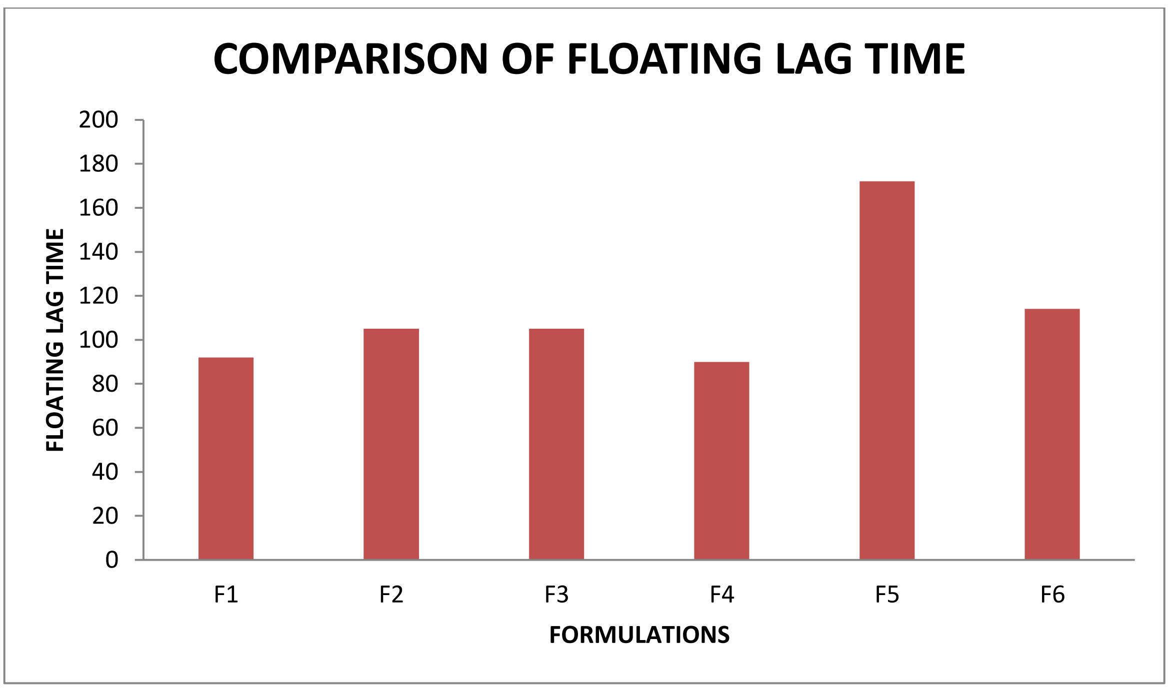


Table no 23 : Data for Drug content uniformity

Formulation code	Drug content (%)
F-1	95
F-2	85
F-3	97
F-4	100
F-5	102
F-6	99

Fig no18: Comparison of drug content

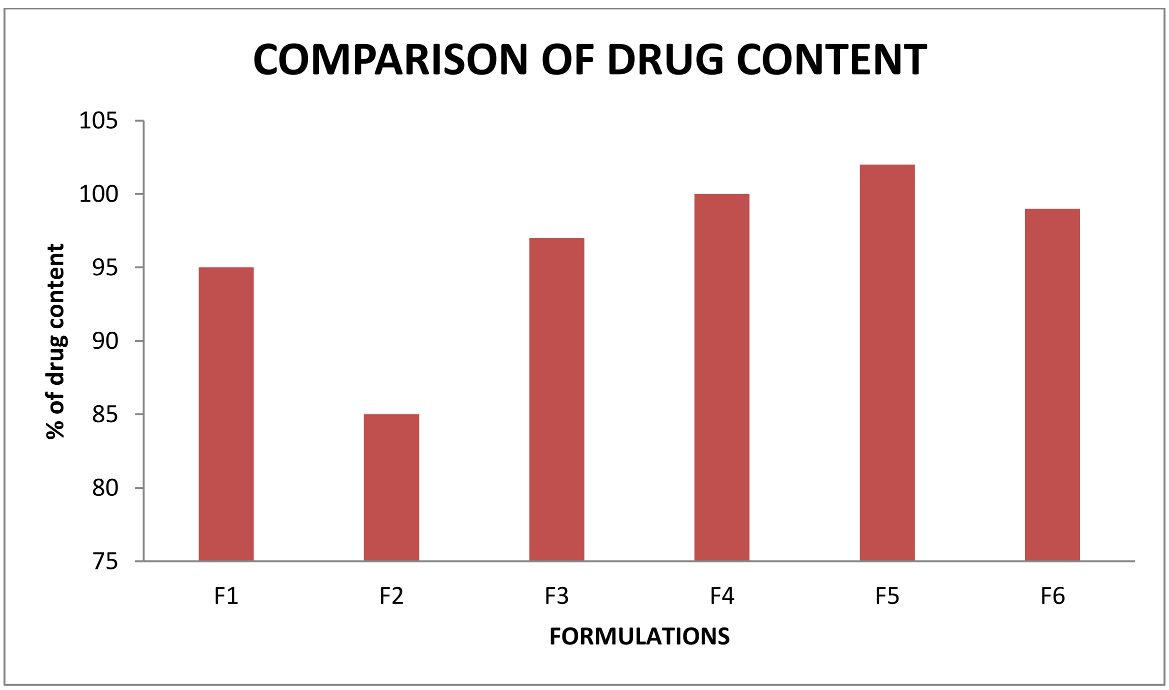


Table no24: DISSOLUTION TABLE FOR F1

s.no	TIME(HRS)	%DRUG RELEASE
1	1	4.9
2	4	39.4
3	8	63.2
4	16	62.7
5	20	83.5

Fig no:19 Dissolution profile -F-1

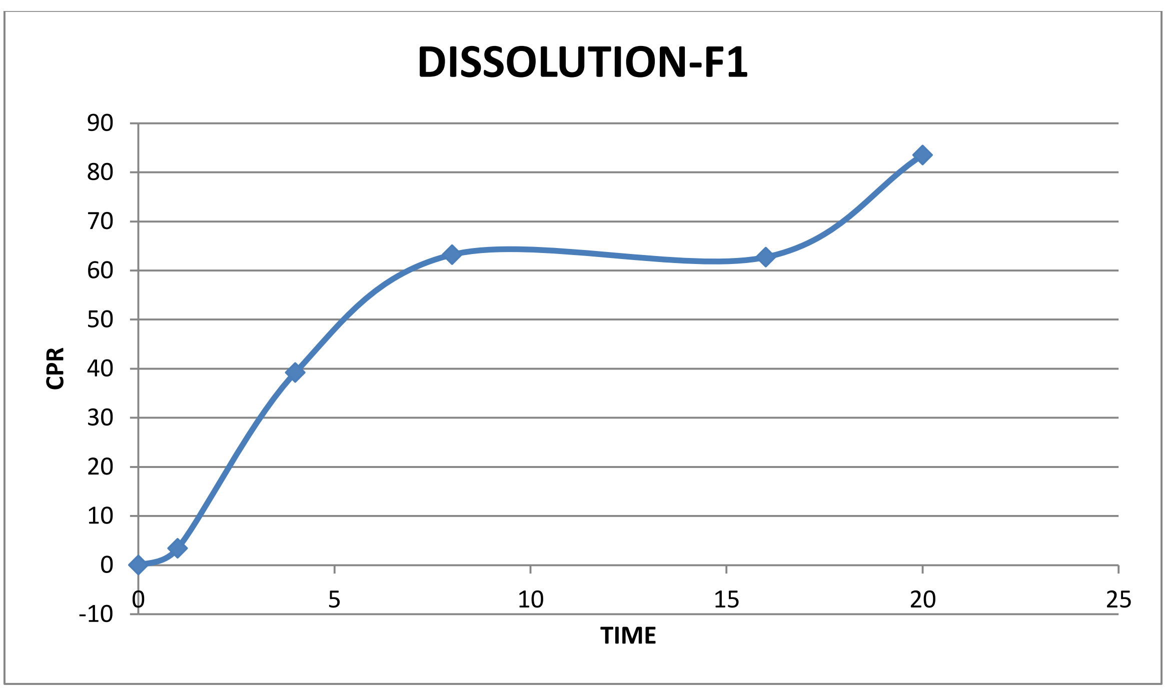


Table no 25 :DISSOLUTION TABLE FOR F2

s.no	TIME(HRS)	%DRUG RELEASE
1	1	6.8
2	4	34.1
3	8	54.3
4	16	65.7
5	20	93.9

Fig no20:Dissolution profile -F2

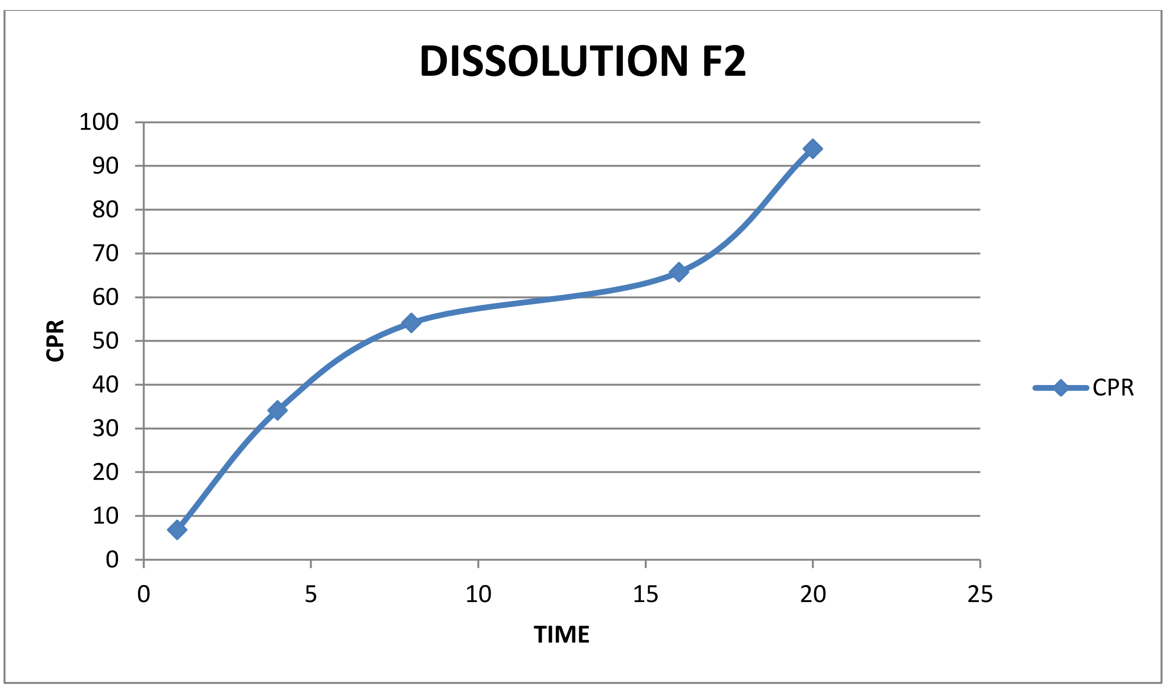


Table no:26 Dissolution table for F3

s.no	TIME(HRS)	%DRUG RELEASE
1	1	3.4
2	4	39.2
3	8	58.6
4	16	71.3
5	20	93.9

Fig no21: Dissolution profile F-3

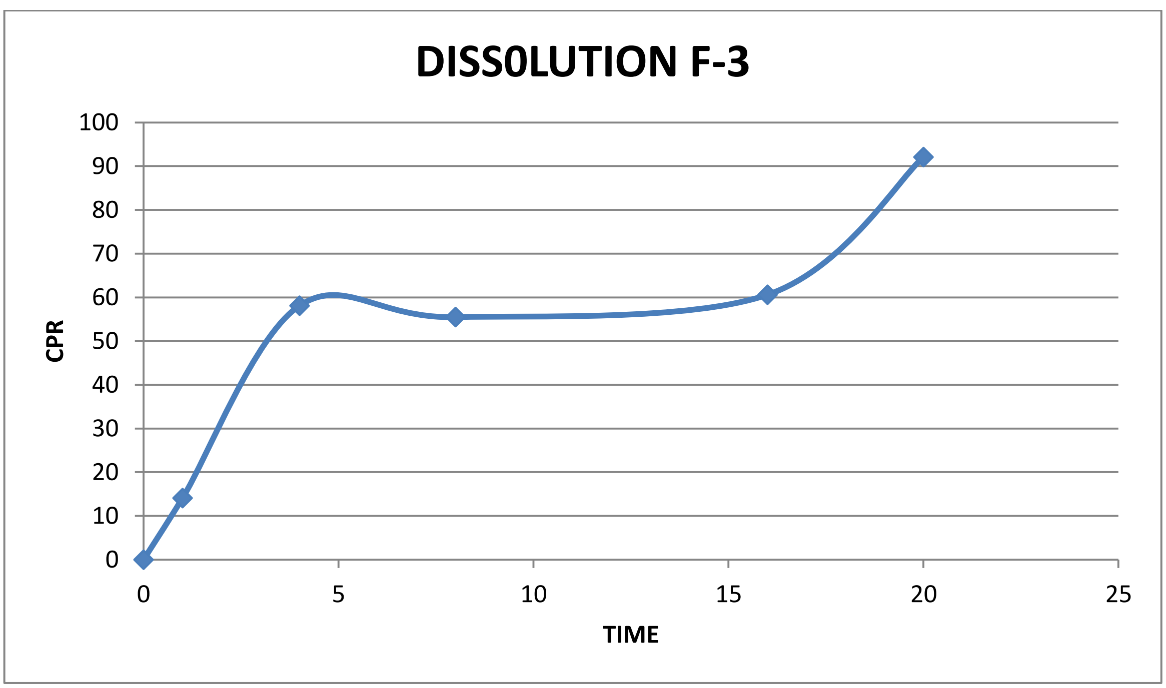


Table no 27: DISSOLUTION TABLE FOR F-4

s.no	TIME(HRS)	%DRUG RELEASE
1	1	14.1
2	4	58.3
3	8	55.7
4	16	60.6
5	20	92.1

Fig no22:Dissolution profile F-4

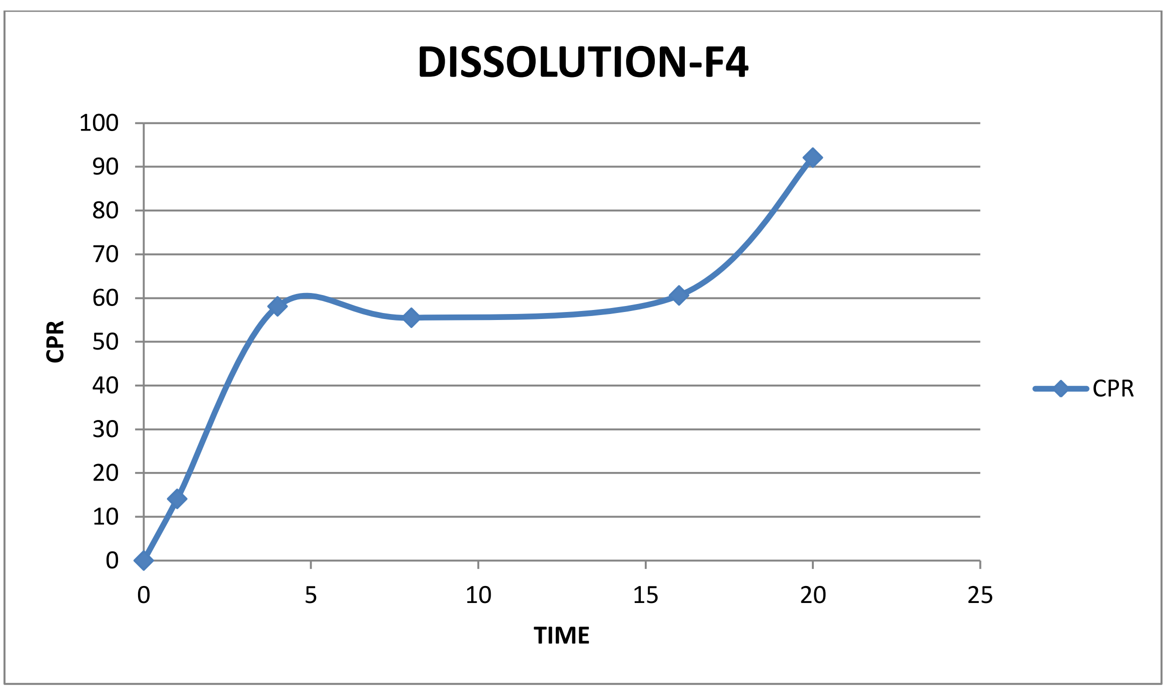


TABLE NO:28 DISSOLUTION TABLE FOR F5

s.no	TIME(HRS)	%DRUG RELEASE
1	1	7.7
2	4	34.1
3	8	58.6
4	16	62.9
5	20	97

Fig no23: Dissolution profile F-5

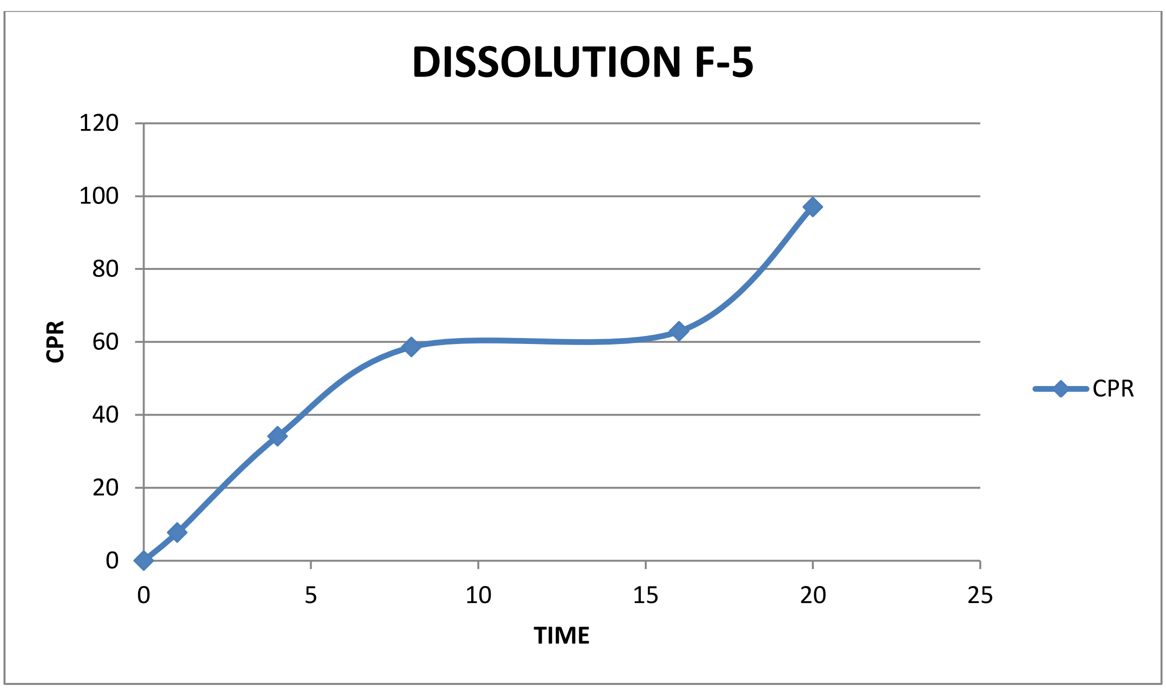


Table no29: DISSOLUTION TABLE FOR F6

S.N0	TIME(HRS)	%DRUG RELEASE
1	1	17
2	4	58.3
3	8	55.7
4	16	60.6
5	20	92.1

Fig no 24:Dissolution profile F-6

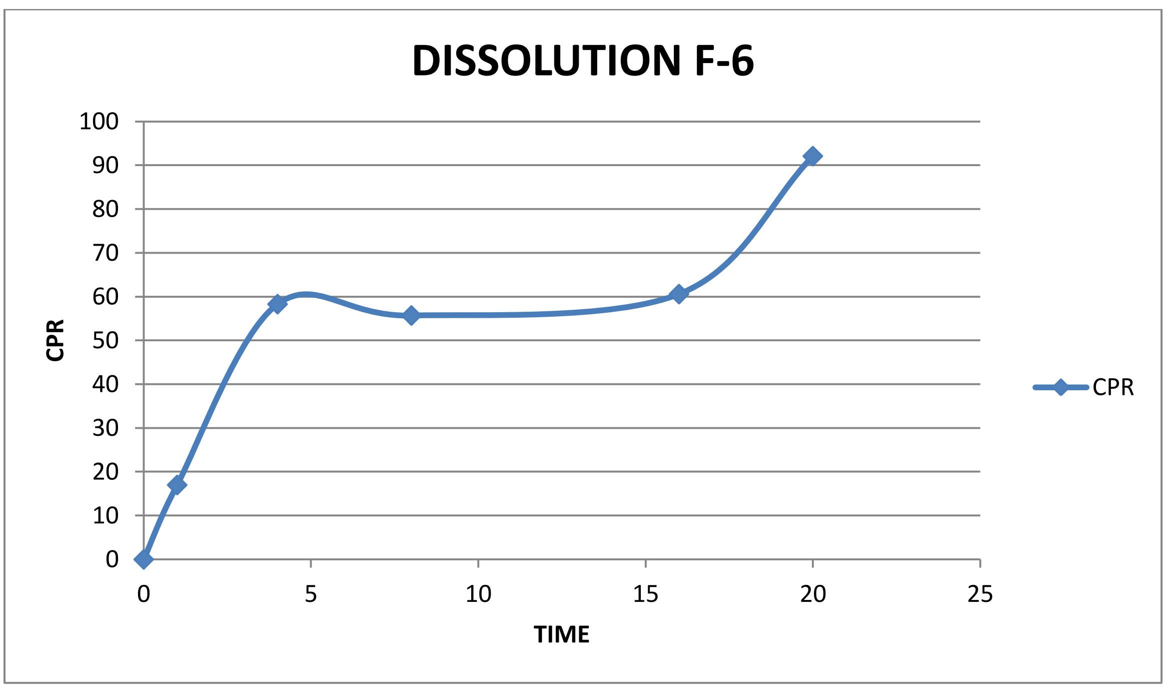
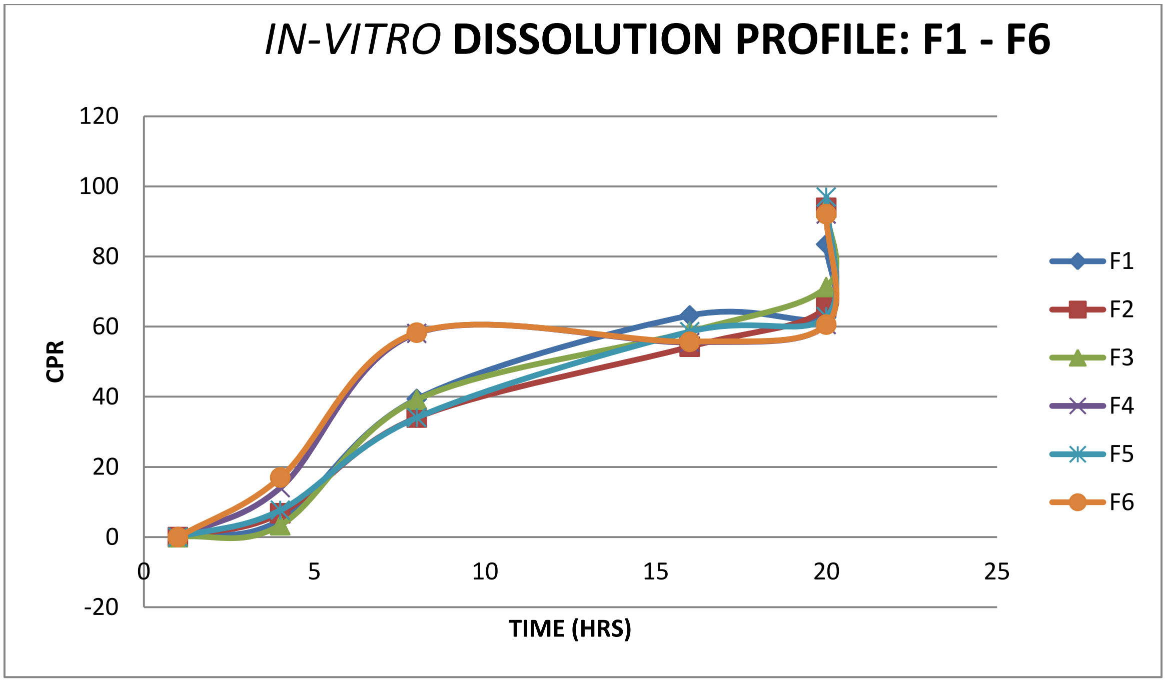


Table no:30 Cumulative percentage of of all the formulation(F1-F6)

FORMULATION	1HR	4HR	8HR	16HR	20HR
F1	4.9	39.4	63.2	62.7	83.5
F2	6.8	34.1	54.3	65.7	93.9
F3	3.4	39.2	58.6	71.3	93.9
F4	14.1	58.1	55.5	60.6	92.1
F5	7.7	34.1	58.6	62.9	97
F6	17	58.3	55.7	60.6	92.1

Fig no25:Cumulative percentage of drug release of all The formulations



STABILITY STUDIES:

Dissolution profile of Losartan Potassium tablets from formulation F5 after 30 days and 90 days at 40±2^{0}c/ 75±5% RH

Table no:31 stability studies of the F5 Formulation

S.NO	TIME(HRS)	INTIALDRUG RELEASE	30DAYS	90DAYS
1	1	7.7	7.4	7.1
2	4	34.1	33.7	33.1
3	8	58.6	58.1	57.1
4	16	62.9	62.2	61.9
5	20	97	96.8	96.75

DISCUSSION:

The present investigation was undertaken to formulate losartan potassium sustained release floating tablets for the treatment of hypertension . Formulations were evaluated for pre and post compression parameter.

The compatibility studies for the drug and excipients used in the formulation were carried out .The FT-IR spectral analysis showed that there was no change in characteristic peaks of pure drug Losartan potassium and excipients which confirmed that the absence of chemical interaction between the drug and excipients. .

6 formulations were formulated by using different proportions of polymers and floating agents. All the formulations were prepared by direct compression . The blend of different formulations were evaluated for angle of repose ,bulk density and tapped density , Hausner's ratio, and compressibility index. The results showed that all the formulations of powders were within the limits and thus it confirmed that the powders have a very good flow property .

The results of post compression such as thickness , hardness , friability ,weight variation and drug content and floating log time for the prepared formulation were within the limits .

In the formulations F1,F2 ,F4 and f6 f3 ,the polymer ratio is used in much quality and the results in less release of drug is seen at the time of dissolution where as the drug coated with less polymer show a very good release dissolution release profile rate than other formulations and given best results .

In the formulation F5 prepared with HPMC E15 200mg and MCC 65mg in sufficient quantity showed maximum (97%) in-vitro drug release at the end of 20 hrs . Although all the formulations shown a good release in-vitro release profiles even more than 90% .

The stability study studies has been carried out for the best formulation F5 at 40 ± 2^0C/75±5% RH as per ICH guidelines for three month .Finally the drug is assayed for content uniformity and weight variation and cumulative percentage of drug release show no characteristic change .And hence prepared formulation found to be stable .

In the present work efforts have been made to developed Losartan potassium sustained release floating tablets was depend upon polymer and floating agents ratio . The results showed that the *in vitro* drug release depend upon the concentration of polymer and floating agents used .The best (f5) formulation contain sufficient quantity of HPMC E15 and MCC and *invitro* drug release is compared with the other formulations .

SUMMARY AND CONCLUSION

Losartan potassium tablets used for the treatment of hypertension.

Losartan potassium tablets were successfully formulated by using different concentration of polymers (HPMC E 15, HPMC K15,MCC , MG.STERATE and ,Sodium bicarbonate ,citric acid and TALC) to sustain the drug for a prolonged period of time .

FTIR study performed for identification and compatability study of drug and exepients , found no characteristic change in drug-excipient powder mixture. Hence the excipients were selected for the formulation development.

Powder blends were evaluated for tests, such as bulk density, tapped density, compressibility index and Hausners ratio before being punched as tablets.

The *In-vitro* dissolution profiles of F1 to F6 were found to have different percentage of drug release .The percentage of drug release is low (83.5) for F1 tablets when compared to other formulations .F5 has better percentage drug release profile with maximum (97%)at the end of 20^{th} hr sustained action .The F5 formulation was fabricated with a very less polymer ratio and show a very a good release profile at the end of $2O^{th}$ hr.

The optimized batch tablets , stability studies are carried out for three months ,as per ICH guidelines (40 ± 2^{0}C/RH75±5).Tablets were evaluated for assay and in-vitro dissolution, but found no significant change during the study period .

CONCLUSION :

It can be concluded that sustained release tablets of Losartan potassium can be performed by direct compression method .All the formulas show a very good drug release profiles and shown better sustained action till the end of last hour (20^{th} hrs) .And hence will improve patient compliance and increase in bioavailability.

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